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REVIEW ARTICLE

Consanguinity, Fertility and Reproductive Outcomes: An International Review

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ABSTRACT

Consanguineous marriages have been common throughout human history, and remain so even today in many parts of the world. Many Arab countries display some of the highest rates of consanguinity and, specifically, first cousin marriages which may encompass 25 to 30 percent of all marriages.
The effects of inbreeding on reproductive outcome have been extensively studied. It used to be generally believed that inbreeding contributed to increased mortality and morbidity with detrimental effects on reproductive outcome; however, some studies have shown only a moderate to slight impact. The fertility of consanguineous couples and infant and childhood morbidity and mortality in their progeny have also been extensively studied and numerous studies have concluded that consanguinity is not associated with either a significant positive or negative effect on fertility.
The majority of studies found that first cousin couples produce more children. In many cases the mean number of live births to women in consanguineous marriages has been reported as being higher than that in non-consanguineous unions, although several studies found that mean fertility rates may be lower in consanguineous couples. In general, higher total fertility rates have been reported in consanguineous marriages. Reports regarding the association of consanguinity and fetal wastage are conflicting, with some reporting that the total prenatal losses were essentially the same for consanguineous and non-consanguineous.
Congenital malformations have long been established to be higher in consanguineous couples above the background rate (4.5% vs 1%). Due to the principle of the existence of a common ancestor. Consanguinity is most commonly associated with inborn errors of metabolism, most of which are autosomal recessive. Consanguinity also increases the incidence of multi-factorial disorders such as diabetes, cardiovascular disorders, obesity and certain types of cancers, which may in turn affect reproductive outcomes. Pregnancy outcomes, such as increased pregnancy wastage and preterm labor have been reported with consanguineous marriages.
The most significant effects on reproductive outcomes are mostly due to autosomal recessive inherited conditions and inborn errors in metabolism.
In the future, with completion of the study of the whole human Genome and current advances in pre-implantation diagnosis and screening it may be possible to mitigate some of the adverse reproductive outcomes associated with consanguinity.

INTRODUCTION

The word consanguinity is derived from the mistaken notion that blood in Latin "sanguis" is the basis of inheritance. In principle, it can be proved that any pair of human individuals has common ancestors, but to find those of two individuals taken at random, one would usually have to explore their lineage over numerable generations. Thus, it is necessary to introduce a limit to how far back one must seek previous common ancestors in order to consider two individuals as being consanguineous.

The aim of this study was to examine the effect of consanguineous marriage on reproductive performance, in terms of fertility and offspring mortality. The data used for this review are the results of a population-based survey performed during the last decade. These findings are important taking into consideration the positive and negative affects of consanguineous marriages.

A consanguineous marriage can result in children with cognitive difficulties, heart defects, and impaired hearing, as well as other genetically inherited diseases. Conversely, consanguineous marriages are thought to have social and cultural advantages, such as, stable marital relationships, reduced risks of family financial problems, ease of marriage arrangements, improved female autonomy, better compatibility with in-laws, less domestic violence and so on.

Clinically, a consanguineous marriage means the union between couples who are second cousins, or even more closely related.[1,2] Among Muslims and Arabs of other religions, this would include double first cousins, first cousins, first cousins once removed, and second cousins. Uncle-niece marriages are prohibited in Islam but are permissible in the Hindu and Jewish religions. Consanguinity may also refer to unions of individuals with at least one common ancestor, such as those occurring within population isolates, small towns, tribes, intra-community, or endogamous marriages as is the case in Israeli Arabs.[3]

Prevalence and Geographic Distribution

Consanguineous marriages have been practiced for hundreds of years in numerous communities worldwide. Among Muslims and Hindus such marriages continue to take place on a large scale.

Several studies have reported a decline in consanguineous marriages in several locales, such as in Jordan, Lebanon, Morocco, Mauritania and Israeli Arabs. In contrast, others have reported an increase in rates of consanguineous marriages in Qatar, the United Arab Emirates (UAE) and Yemen.[4-7] Such marriages are also practiced in other parts of the world, e.g., Japan and Brazil[8-10] as well as in small, isolated, closed communities, such as the Old Order Amish in the United States of America (USA)[11] and the Samaritans in Jordan and Israel.[12]

Approximately 60-70 years ago, concurrent with the decline of the prevalence of infectious diseases due to the widespread implementation of vaccination programs and antibiotic use, as well as a decrease in malnutrition due to better nutrition, childhood illnesses caused by genetic diseases have assumed far greater prominence.[13]

Among the demographic and social correlates of consanguinity are poor rural communities that have low levels of maternal education, early age at marriage and birth of first child, short birth intervals, and longer reproductive spans.[4,14-16]

Offspring of consanguineous couples represent a significantly large group as an estimated 10.5% of all children worldwide have consanguineous parents.[17] Annually, over 130 million infants are born worldwide[18] which leads to the conclusion that the considerable number of 13.6 million of those children have consanguineous parents.

Population types favouring consanguineous marriages:

1. Major populations in the Middle East, North Africa, and South Asia (20-50% of all marriages are consanguineous);
2. Major populations in Latin America, Japan, and China (1-10% of all marriages are consanguineous);
3. Recent migrants from Pakistan, India, the Middle East, North Africa and South Asia, who have become permanent residents in Europe, the USA and Canada (e.g., 2 million North Africans in France, 1.5 million Turks in Germany, and 0.5 million Pakistanis in the United Kingdom);

Small population isolates where inbreeding is common account for a very small percentage of the world population (e.g. the Amish in the USA).[19]

The type of consanguineous marriage varies in different communities. Consanguinity rates vary from one population to another depending on culture, religion, and geography. The preferred types of consanguineous marriage vary according to tradition. Globally, the most common form of consanguineous marriage is between first cousins, who on average have co-inherited 1/8 of their genes from one or more common ancestors. Therefore, first cousin offspring will be homozygous at 1/16 of all loci, which is

conventionally expressed as a coefficient of inbreeding (*F*) of 0.0625, and is also 0.125, 0.0313and 0.0156 for double first cousins.

The most common types of consanguineous marriages in the Arab population are those between patrilateral parallel first cousins (the children of two brothers), although other variations of first cousin marriages (matrilateral parallel cousins, i.e.. the children of two sisters, and cross-cousins, i.e., children of a brother and a sister) are also practiced, and marriages between more distant relatives also occur.[20] Uncle-niece marriages are the commonest type of union among the Indian population ($F = 0.125$) although first and other cousin marriages are also customary.[21] In the Muslim religion, marriage between an uncle and niece is prohibited, but is permissible in the Jewish religion, as is a first cousin marriage.

First cousin and other more remote categories of consanguineous marriage are permissible under civil legislation virtually throughout the world. However, the USA is a notable exception, with varying forms and degrees of restrictive laws on consanguineous unions in 31 of the 50 states. Some prohibitions on first cousin marriages apply in two other countries, the People's Republic of China and the People's Democratic Republic of Korea.[22] Secular changes in consanguinity rates have been perceived in some Arab populations.

Amongst the factors responsible for the decrease in consanguinity rates in Arab countries are:

1. The population is more aware of the association between genetic diseases and consanguinity;
2. Increasing higher levels of female education;
3. Decline in fertility, resulting in lower numbers of suitable marriageable relatives;
4. Change in the economic status of families and the mobility to urban settings, i.e., Jordan,[7] Lebanon,[23] Bahrain,[24] and among Palestinians.[3,6,25]

HEALTH IMPACT OF CONSANGUINITY

The biological effects of consanguineous marriages have been studied extensively in almost all populations throughout the world.[4,8,17, 21,22, 26-45] It was generally believed that inbreeding contributed to increased mortality and morbidity with detrimental effects on reproductive outcome.[4,21,28,43] However, studies conducted in Brazil and Japan have shown only a moderate to slight impact.[8,35] A prospective study on large numbers of couples showed no detrimental effect of inbreeding on reproduction and mortality, and it was suggested that the adverse consequences of inbreeding may have been eliminated by the eradication of deleterious recessive genes in earlier generations. Unfortunately, not all published studies have taken into account possible sources of bias mainly socioeconomic status and other confounding factors[4,13,28,32,35,43,46,47] namely, maternal age, maternal education, birth intervals and birth order. These variables have been shown to have an adverse impact on infant and 5-year survival.[14]

Consanguinity and reproductive behavior

The influences of consanguinity on reproductive behavior are shown in Table 1.

Table 1. Reproductive behavior and consanguinity[22]

Various behavioral factors	In consanguinity
Mean maternal age	Lower
Mean maternal age at first birth	Generally lower
Time-span of child bearing years	Longer partly due to lower contraceptive usage
Maternal-fetal genetic compatibility	Enhanced and essential for fetal growth and development
Rates of rhesus incompatibility	Lower
Pre-eclampsia	Equivocal
Successful pregnancies and surviving children	Larger number
Mean number of live birth in 40 studies	First cousin couples had a larger mean number of live births in 33 studies which is an additional 0.08 birth per family
Icelandic reproductive success	Iceland reproductive success was greatest even at a level of parental relatedness approximating to third to fourth cousins. It was suggested that a significant underlying biological contribution to the enhanced fertility of at least some consanguineous couples

Consanguinity and fertility

The main outcomes of consanguinity most extensively studied are the fertility of consanguineous couples, and infant and childhood morbidity and mortality in their progeny. A majority of studies indicated that first cousin unions procreate more children, a finding usually explained in terms of a younger start at the reproduction process and to reproductive compensation, i.e. the replacement of children who die at an early age.[48]

The association of congenital malformations and consanguinity is well known. The detrimental health effects that are associated with consanguinity are mainly caused by the expression of rare genes inherited from a common ancestor. The fact that increased levels of morbidity and mortality occur due to the expression of rare genes has been extensively reported.[4] Nonetheless, little is known about the effects of inbreeding on reproduction and fertility in modern human societies. It appears that biological effects are masked by socioeconomic factors, that are the major determinants of fertility.[49] Reports in the literature on fertility and consanguinity are contradictory.[23,41,48,50-63]

A survey by Hussain and Bittles[50] was a review of 21 studies performed in India and Pakistan that found substantial variations in mean fertility levels. In most cases the mean number of live births reported by women in consanguineous marriages was higher than that in nonconsanguineous unions. Notably, in 19 of the 21 studies, women in first cousin unions had a higher mean number of live births compared to nonconsanguineous couples.

Several other studies indicated that mean fertility rates may be lower in consanguineous couples.[49,60,64-68] Conversely, other reports suggested that lower fertility was possibly due to a failure to initiate pregnancy when the couple shared specific HLA haplotypes,[69] or because of the expression of deleterious genes acting during early embryonic or fetal development that result in periconceptual losses.[70] Mechanisms, such as greater genetic compatibility between the mother and developing fetus in a consanguineous pregnancy could lead to reduced rates of involuntary sterility and prenatal losses, and the strong possibility that greater fertility may exist in consanguineous unions as a compensatory mechanism for infant and childhood losses.[71-73]

In general, higher total fertility rates have been reported in consanguineous marriages.[59,61-64,74-83]This could be explained partly by lower parental age at marriage, and partly by the age of the closely related couples at the birth of their first child[4,83] (Table 1). Furthermore, the time interval between the marriage and the first pregnancy is often longer in consanguineous unions, possibly due to gynecological immaturity in females who marry at a young age. Subsequent intervals between births are usually shorter, and consanguineous couples may continue their childbearing until a comparatively more advanced age.[72] Another reason is that consanguineous couples may also be less likely to use reliable methods of contraception.[64]

Various studies have indicated that consanguinity was not found to be associated with either a significant positive or negative effect on fertility. [23,41,48,50-59]

Tadmouri et al.[3] reported that in the Arab population, higher rates of both fertility and live births were found among first cousin couples when compared with than nonconsanguineous couples in Qatar,[62] Tunisia,[63] Kuwait,[84] and Saudia Arabia.[85]

Moreover, in various ethnic groups in Mauritania, consanguineous couples had significantly higher averages of fertility than those of nonconsanguineous couples.[81]

Khlat investigated the effects of consanguineous marriages on fertility and mortality of offspring in Beirut through a population-based health survey of 2,752 households.[23] The total number of pregnancies, live births and living children were significantly higher among consanguineous than nonconsanguineous couples and no difference was found either in fertility or mortality when allowance was made for socioeconomic status, religious affiliation and marriage duration. The lack of a significant pattern in the final analysis was attributed to the longstanding practice of consanguineous marriages. A more recent study from Lebanon suggested a positive association between consanguinity and male factor infertility among 120 infertile males, indicating the important contribution of recessive genetic factors to the etiology of male infertility.[68]

Bhasin and Nag evaluated the incidence of consanguinity and its effects on fertility and child survival among the Muslims of the Ladakh region in Jammu and Kashmir. These authors compared the study populations with other Indian Muslim population groups and found that the incidence of consanguinity was relatively low. They also reported increased fertility and decreased proportion of surviving children in consanguineous compared with nonconsanguineous marriages.[77]

Postma et al. conducted a survey among the inhabitants of a small and isolated Swiss

village and estimated the level of inbreeding and relatedness of both spouses of all married couples. They found that although related couples did not have fewer children themselves, their inbred daughters provided them with fewer grandchildren.[65] The association of consanguinity and fertility is shown in Table 2.

Table 2. The effect of consanguinity on fertility – Study populations and consanguinity

Location	Population	Consanguineous Marriage (CM) (%)	No. of women	Fertility	
Ladakh region in Jammu and Kashmir	Indian Muslim population groups	14.8-21.8	503	Increased fertility in CM than in non-CM	77
South and Southeast Asian countries	Prevalence of CMs in these countries followed by an assessment of the association between consanguinity and fertility.	Consanguinity was found to be associated with number of direct and in-direct determinants of fertility	Higher fertility among women in the first-cousin unions compared to those married to non-relatives	The association between consanguinity and fertility was assessed reviewing published literature from data in Pakistan and India	86
Algeria	Arab- Muslims	33.33% with a slight preference between first cousins	123	Observed increased fertility, early marriage age, significant association between consanguinity and reproductive health	87
Data were picked from different data BASE /regions such as PUBMED, CINAHL, Web of Knowledge and Google Scholar	Different communities	Wide range of incidence of consanguinity	Rates ranging from 80.6% in certain provinces in the Middle East to less than 1% in western societies.	These may in turn affect reproductive outcomes. It may also affect fertility rates. Pregnancy outcomes, such as increased pregnancy wastages and preterm labor have been reported with consanguinity.	88
Pakistan Demographic Health Surveys carried out from 1990-2018	Secondary data analysis using all four waves of the survey	About 63% during last three decades	Consanguinity is strongly associated with socio-demographic characteristics and womens' reproductive health and fertility in Pakistan		89
Pakistan	Muslims	56%- 75%	13,558 married women	The conclusion of the study was in order to understand the linkage of CM and the impact of fertility outcomes there is a need to further explore the factors that enhance the implication of CM and its correlates	90
Okara District, Pakistan	Cross-sectional study	61%	1521 year 2016-2017	Women having consanguineous unions (CU) had significantly higher mean fertility, mean live births compared with subjectsf having NCU	91
Visakhapatnam district of Andhra Pradesh, Khond	Cross-sectional study	ICF=0.0439	Authors found that of sample of 247 number of married women, 167 preferred CM and remaining 80 women preferred non-CM.	All fertility components are higher for CM couples compared to non-CM	92
Canada	Canadian women born in the late 19th century	Inbreeding and fertility in Canadian women in the late 19th century	172 women born in 1879	The effects of inbreeding on fertility in these Canadian women showed that inbreeding depression affects reproduction in modern societies through an interaction with age.	49
Turkey (Goode's foundational work on the fertility transition identified own-choice marriage)		This study evaluates Goode's theorized connection using pooled Demographic and Health Survey data from Turkey	19,200 women	The results were own choice marriage leads to fertility decline	93

Fertility and consanguinity in India

Similar to studies from other parts of the world, those for India lack a unanimity of opinion among experts concerning the effect of consanguinity on fertility. There exist two contradicting viewpoints: one of a positive effect on an increased fertility rate[59,76-78] and the other, showing no clear-cut association with fertility.[48,56-58]

Twenty-one studies in India and Pakistan revealed that in most cases the mean number of live births reported by women in cousin marriages

was higher than that in non-consanguineous unions,[50] in particular, for women in first cousin unions having a higher mean number of live births, compared to non-consanguineous couples, in 19 of the 21 studies cited.[50]

Asha Bai et al.[59] found that fertility in southern India was higher in consanguineous than in non-consanguineous marriages, but the number of living children was approximately equal in both groups because of increased child mortality in the consanguineous group ($p<0.05$). The frequencies of abortion and stillbirth were also approximately equal in both groups, but the frequency of congenital anomalies was significantly higher among the offspring of consanguineous parents.

Reddy et al.[60] assessed the association between consanguineous marriages and fertility in three caste groups in Andhra Pradesh, India. Overall, the consanguineous marriages were significantly more fertile than the non-consanguineous unions. Conversely, these authors) examined data from 1,500 women belonging to three endogamous communities of Chittoor District, Andhra Pradesh, India. Five hundred women from each community participated in the survey. These authors postulated that due to inbreeding, the offspring of earlier generations may have passed on deleterious genes to later generations, resulting in a negative aspect of reproduction among the offspring of the present couple.

Yasim Naidu et al.[78] collected data on patterns of marriage, differential fertility and mortality from 211 Kotia women residing in the Visakhapatnam district of Andhra Pradesh, India. Women in consanguineous marriages had a lower mean number of total conceptions, live births and living offspring (net fertility rate).

In a study in Bangalore Karnataka in southern India, Devi et al.[57] found that 29% of 3,350 marriages were consanguineous. These authors did not find any significant differences between the consanguineous and non-consanguineous groups regarding the numbers of live born, or living children. Verma et al.[58] reported a study conducted in 1978 in which data on 1,000 mothers in the Indian district of Pondicherry were analyzed. Their findings revealed that consanguinity did not affect overall fertility rates, but rather contributed considerably to infant mortality and morbidity.

Basu[56] studied endogamous Muslim groups in Delhi and Lucknow, India. In all groups, the fertility rate was higher in consanguineous than nonconsanguineous marriages. However, the net fertility rate was not higher.

Bittles et al.[48] collated, from a systematic review of the literature, data on 30 populations residing in six countries, and found a positive association between consanguinity and fertility at all levels of inbreeding, attaining statistical significance at first cousin level ($p < 0.0001$). In net terms, consanguinity was not found to be associated either with a significant positive or negative effect on fertility.

In summary

Most studies have shown similar or higher fertility rates among consanguineous versus non-consanguineous couples. This may be attributed to skewing factors in the statistics, including younger age of females at marriage and perhaps associated fewer years of schooling and less sophisticated reproductive knowledge among the consanguineous group, leading to increased maternal reproductive span, yet with a higher infant mortality rate among them, evening out the numbers when comparing with the lower prenatal losses to begin with among nonconsanguineous couples.

Fetal Wastage

Reports regarding the association of fetal wastage and consanguinity are conflicting according to studies from Sudan, Saudi Arabia and Jordan. In Saudi Arabia,and Jordan the total prenatal losses were essentially the same for consanguineous and nonconsanguineous couples.[41,55,94]

Other studies have reported similar results.[23,51,62,63,95-98]

However, a higher rate of prenatal losses among consanguineous couples was observed in the Palestinian Territories.[99]

The possible effect of consanguinity on abortion rate and still births is shown in Tables 3 to 5.

Table 3: Rates of abortion associated with consanguinity

Location	Abortion rates %			Ref.
	First cousins	**Distantly related**	**Unrelated**	
Van Region Eastern Turkey 2005-2006	High rate of abortion was found in families of consanguineous marriages (CM)			100
Lebanon	21.5%	-------	16.1%	101
Kahramanmaras City, Turkey,	The rate of spontaneous abortion was similar in the CM and non-CM groups			102
Karachi, Pakistan	The risk of an adverse pregnancy outcome was higher among the progeny of couples who were not only themselves consanguineous but also offspring of consanguineous unions			103
Turkey	9.3%	8.2%	4/0%	104
Lahore, Pakistan	Increased rate of spontaneous abortions, childhood deaths			105
Japan	No significant difference was observed between CM and non-CMs			106
Chicago, USA	14.5%		12.9%	107
Kalaburgi, Karnataka, India	Prevalence of abortions and preterm deliveries was noted to be 60% and 64.28% respectively in CMs. Maternal and child morbidity were more prevalent in CMs compared to non-CMs			108
Military Hospital Quetta, Pakistan	Difference between stillbirth and abortion among CMs and non-CMs was significant. Large population-based studies are needed before declaring consanguinity as a health problem in this setting			109
Nation-wide Survey India	Relative risk of stillbirth, abortion, miscarriage and spontaneous miscarriage were higher among consanguineous mothers compared to non-consanguineous mothers			110
Rural Tamil Nadu India	Abortions were found to be more common in CMs			111
India	Mean number of abortions in consanguineous group were 0.4%, and 0.1% in nonconsanguinous group. The difference is statistically significant.			112
General	Same or lower rates of abortion			113

The majority of surveyed locations across the world showed significant differences in spontaneous abortions\ miscarriage rates among close consanguineous vs. distant and non-consanguineous marriages, and appear to transcend socio-economic and cultural factors. Hidden factors not sufficiently elucidated possibly affecting local statistics compared to worldwide figures appear to lie in an additive influence by repeat-generation consanguineous in-breeding affecting pregnancy and fetal viability.

Table 4. The rates of stillbirths associated with consanguinity

Location	Stillbirth rates %			Ref.
	First cousins	Distantly related	Unrelated	
Van region eastern Turkey 2005-2006	High stillbirth rate found in consanguineous marriages (CMs)			100
Iran 2015	CM is associated with increased risk of stillbirth, particularly preterm stillbirth. Findings for other maternal risk factors for stillbirth in rural Iran are consistent with previously reported findings from high-income countries			114
Westmead Sydney Australia	Percentage of consanguinity in Westmead stillbirth population from 2005–2010 was 3.6%-13.0%.			115
Egypt	Stillbirths, child deaths and recurrent abortions were significantly increased among consanguineous parents (80.6%, 80%, and 67% respectively) than among Non- consanguineous parents.			116
Turkey	There was an effect of consanguinity on stillbirth rate			102
Rural Tamil Nadu, India	Stillbirth was found to be more common in consanguineous marriages			111 From abortion table
Pakistan	Difference between stillbirth and abortion among CMs and non- CMs was significant while that of Rh-incompatibility was nonsignificant			109
Australia	Consanguinity was an independent risk factor for stillbirth with a relative risk of 2.88 P < 0.001, 95% CI 1.98, 4.18.			117
Australian Tertiary Hospital	Stillbirth, threatened premature labour, fetal congenital abnormality, perinatal mortality and neonatal outcomes			117
Northern Coastal Sweden	First cousin couples had higher rates of stillbirths and more deaths in infancy and early childhood among their progeny			118
Luton, Pakistan	High rates of stillbirth in Luton, consanguineous Pakistani babies.			119
Kinaye of District Belgaum North Karnataka South India	No significant effect of consanguinity was noted on the rate of abortion, stillbirth, mortality and congenital malformation			120
National Survey Turkey	Consanguineous marriage frequencies were higher $p<0.001$ for women who had spontaneous abortions and stillbirths or who had given birth to infants with a congenital abnormality			121
Oslo, Norway	The risk of recurrence of stillbirth and infant death is higher for offspring of first cousin parents compared with offspring of unrelated parents.			122
Norway	Consanguinity influences stillbirth and infant death independent of maternal education			123
Saudi Arabia	8.3%	------	8.9%	124
	Perinatal and postnatal mortalities were not significantly different between consanguineous and non-consanguineous families.			
Turkey	2.3%	2.1%	1.2%	104
Japan	No significant difference was observed between consanguineous and non-consanguineous			106
Chicago, USA	1.4%	1.2%	------	107

The uncomfortably close overlap between miscarriages and still births for the locales surveyed in Tables 3 and 4, plus their respective adherence to the degree of intra-familial distance, emphasizes the impact of consanguinity on over-all reproductive hardiness. In Table 5 neonatal mortality figures follow similar patterns of risk as a function of the degree of genetic relatedness, even in locales such as Turkey, Kuwait, Israel (and by association the Palestinian Authority), with relatively better access to good neonatal care units, balancing out possible socio-economic factors at play in other locales, such as Sudan, Pakistan and Egypt.

Table 5. The rates of neonatal deaths associated with consanguinity

Location	**Neonatal death rates %**			**Ref.**
	First cousins	Distantly related	Unrelated	
Karachi, Pakistan	Consanguinity is a risk factor for neonatal mortality			103
Saudi Arabia	%2.7	-------	%2.2	124
Israel (Arab)	1.6%	0.6%	0.9%	97
Sudan	No significant difference was observed between consanguineous marriages (CMs) and non-CMs			41
Turkey	18.9%	14.9%	10.8%	104
Alexandria, Egypt	Consanguinity increased the relative risk of neonatal death and total reproductive losses			98
Kuwait	3.1%	2.7%	2.5%	96
South India	5.2% includes uncle/niece unions	3.7%	4.0%	36
Japan	No significant difference was observed between CMs and non-CMs			106
Rural Tamil Nadu India	Neonatal birth was found to be more common in CMs			111
Tunisia	17.4%	7.4%	75.2%	63
	Higher rates of neonatal and post-neonatal deaths, and deaths of children younger than 5 years were observed in consanguineous couples			
East Jordan	17.1% all deaths in the first year of life	15.1% all deaths in the first year of life	12.9% all deaths in the first year of life	125
Chicago, USA	1.9%	-------	1.8%	107
India	No significant effect of consanguinity was observed on the number of stillbirths, neonatal mortality, obstetrical complications and congenital malformations			112
Qatar	Neonatal mortality rates in Qatar declined very little between 2008 and the first quarter of 2011.			126
Rural areas in Iran	Familial marriage to first cousins is considered as an important risk factor for neonatal death			127

A consanguinity study group of international experts and counselors met at the Geneva International Consanguinity Workshop on May 3, 2010, and their deliberations on the known and presumptive risks and benefits of consanguineous marriages indicated that:

1. Consanguinity does not seem to be associated with elevated rates of miscarriages and in general, abortion rates among consanguineous and nonconsanguineous couples are comparable;
2. A large majority of studies have failed to detect any significant increase in fetal loss rates among consanguineous couples (Table 3). Available data suggest that stillbirth rates are either similar, or slightly higher among consanguineous couples. A meta analysis of stillbirths showed a mean excess 1.5% deaths among first cousin progeny.[45]
3. First cousins had a higher mean number of live births in 33 of the 40 studies, which translated into a mean 0.08 additional births per family.[22]
4. Studies among first cousin offspring also indicated a mean 1.1% excess in infant deaths compared with nonconsanguineous progeny.[22] with an equivalent excess of 3.5% in overall prereproductive mortality.

Bittles and Black[17] investigated the impact of consanguinity on death from ≈6 months gestation to an average of 10 years of age. Using a meta-analysis, they compared the prereproductive mortality in first cousin versus nonconsanguineous progeny within specific populations. The study sample comprised 69 populations resident in 15 countries located across

four continents, with a total sample size of 2.14 million. The results revealed a mean excess mortality at first cousin level of 3.5% (r2 = 0.70; p < 0.00001).

The estimate of 3.5% excess deaths among first cousin progeny compares with a previous estimate of 4.4% excess mortality[128] calculated from 38 studies, each of which was included in the 1994 analysis. These figures are consistent with the 3.5% excess mortality derived from Italian data in the - early to mid-20th century[129] (Table 6).

Table 6. The rates of infant deaths associated with consanguinity

Location	**Infant death rates (%)**			**Ref.**
	First cousins	**More distantly related**	**Unrelated**	
The Netherlands – Native and Migrants	Between a quarter and a third of marriages are between first cousins. Hereditary causes of death in the Moroccan and Turkish populations are 4-5 times higher than in the Surinamese/Antillians and indigenous Dutch			130
Abu Dhabi United Arab Emirates	Consanguinity is significantly associated with mortality in infants and children aged under 5 years but not with neonatal mortality			131
Israel	The incidence of congenital malformations and Mendelian diseases correspond to the differences in the consanguinity rates between the Jewish and Arab populations			132
Norway	The risk of recurrence of stillbirth and infant death is higher for offspring of first cousin parents compared with offspring of unrelated parents			122
Israel (Arabs)	6.3%	0%	1.3%	97
Rural Tamil Nadu India	A statistically significant positive association was found between the consanguinity and congenital anomaly, prenatal and postnatal loss except in the case of childhood deaths (1–5 years)			112
Palestine refugees in Gaza, West Bank, Lebanon, and Jordan	Infant mortality in the four areas combined was 20·7% (95% CI 18·0–23·7) per 1000 live births in 2006 and 18·0% (15·4–20·6) in 2011. Neonatal mortality in 2006 (14·0 per 1000 live births, 11·8–16·4) was similar to that in 2011 (13·7, 11·5–16·0). Potential risk factors for infant death were preterm birth (odds ratio 6·5, 95% CI 3·5–12·0), low birthweight (3·1, 1·6–6·2) and consanguinity (2·5, 1·8–3·6).			133
Prof. Hanan Hamamy Geneva Foundation for Medical Education and Research	There is a positive association between parental consanguinity and increased infant and childhood mortality			113
Turkey	There is a causal relationship between CMs and infant mortality.			134

Congenital anomalies and consanguinity

Approximately 3-5% of all live newborns have a medically significant birth defect. The recent report by the March of Dimes estimated birth defects to be >69.9/1000 live births in most Arab countries[10,130-132, 135] as opposed to <52.1/1000 live births in Europe, North America and Australia.[3,41] These anomalies are mostly attributable to autosomal recessive diseases.[3,136-138]

Rare and novel autosomal recessive diseases have been widely reported from communities with high consanguinity rates.[139] An increased 2% risk that first cousin couples will bear a child with an autosomal recessive disorder indicates that approximately 8% of these couples have an increased risk of 25% or more, whereas 92% of first cousin couples will not be at high risk of the birth of an affected child. [140-145]

A higher prevalence of birth defects has been reported among first cousin couples in all populations, but the excess rates among first cousin progeny have varied from 0.7% to 7.5%, with differing confounding factors. There is a significantly increased risk of specific congenital heart defects in first cousin offspring which could suggest a recessive mode of inheritance.[146] Elevated rates of consanguinity have been

consistently reported for congenital heart defects, in particular, atrial septal defect and ventricular septal defect, suggesting the involvement across populations of recessive gene variants with similar phenotypic outcomes. In other abnormalities, the results varied between study centers, indicating that population-specific mutations may have been responsible. Conversely, the overall incidence of congenital heart disease among 140,000 newborns in Oman, a country with a high consanguinity rate, was similar to that reported from developed countries in Europe and America.[147] A positive association of consanguinity with cleft lip and/or palate was reported in the Palestinian[148] and Lebanese populations.[3,149]

Consanguinity rates were noted to be higher among parents of newborns with congenital hydrocephalus[150] and neural tube defects[150,151,] than in the general population in some studies, but not in others.[152]

Nevertheless, the association of consanguinity with major congenital malformations, including non-syndromic neural tube defects and cleft lip and/or palate remains controversial.[150-152]

Elevated frequency of Down syndrome has been reported in some populations, e.g., in an Arab village in Israel. Nonetheless, most of the literature on the effects of parental consanguinity on Down syndrome has concluded that no such association exists. A recessive gene coding for non-disjunction of chromosome 21 was proposed to explain the apparent excess of Down syndrome babies born to younger consanguineous parents in Kuwait, but the existence of such a predisposing gene for trisomy 21 has been disputed in other populations.[148]

Childhood deafness has been commonly associated with consanguinity and in the UAE 92% and 57%, respectively, of cases of non-syndromic and syndromic deafness were attributed to autosomal recessive inheritance.[153]

Autosomal recessive retinitis pigmentosa is a more common finding in populations where intrafamilial marriage is favored, and increased rates of congenital cataracts also have been reported in several populations. Nonetheless, consanguinity-associated blindness is rare. According to the Latin American Collaborative Study that examined 34,102 newborn infants, a significant association with consanguinity was found only for hydrocephalus, postaxial polydactyly and bilateral cleft lip with or without cleft palate.[154]

The influence of first cousin marriages on the prevalence of autosomal recessive single-gene disorders was evaluated in a Pakistani community in the United Kingdom.[155]

The results of a 5-year prospective study indicated that there would be a ≈7/1,000 increase in autosomal recessive disorders per 0.01 increase in the mean coefficient of inbreeding.[135]

In a national population, such as Pakistan, where ≈50% of marriages were between first cousins (F = 0.0625)[86] some 22/1,000 extra single-gene disorders could be expected.

Among the Arab populations, either uniformly or in certain locations, there is a specific prevalence of several disorders, such as Bardet-Biedl syndrome, Meckel-Gruber syndrome, spinal muscular atrophy, osteopetrosis and renal tubular acidosis, Sanjad-Sakati syndrome, and negative effects of consanguinity on reproductive health.

Figure

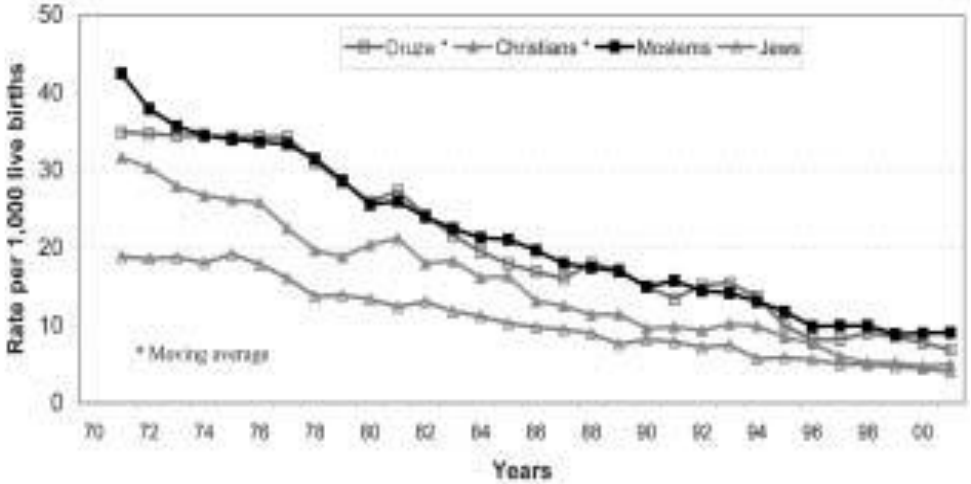

Figure: Trends in infant mortality rate (IMR) according to religion for the years 1970-2000 (rates per 1000 live births). Reproduced with permission from IMAJ.[156]

In 2004, Tarabeia et al.[156] investigated the difference in infant mortality rates (IMR) between the Arab and Jewish populations in Israel, and found that, similar to the Jewish population, the IMR in the Arab community has decreased over the years, although it is still much higher than that in the Jewish community. The continuing difference was attributed to the permanent high rate of consanguineous marriages in the Arab Israeli population,[30] and the association of high rate of major congenital anomalies, of which the central nervous system was the principal affected system.[157]

COMPLEX DISORDERS and CONSANGUINITY

High susceptibility genes may play a significant role in the expression of complex diseases, such as hypertension, coronary artery disease, diabetes, schizophrenia, autism, and cancer. These genetic diseases are passed down according to multifactorial inheritance.[17] If such genes are rare and transmitted in an autosomal recessive manner, then consanguinity could be a determining factor. To date, little has been published on the effects of consanguinity on the complex late-onset disorders that account for most of the global public health burden.[158]

Highly consanguineous populations provide a unique opportunity to detect recessively inherited genes for diseases manifesting later in life, but the association of consanguinity and chronic adult noncommunicable diseases (NCD's) is still not clear. A significant increase in the prevalence of common adult diseases, such as diabetes mellitus, myocardial infarction, bronchial asthma and duodenal ulcer, has been found among offspring of consanguineous marriages.[97,159] However, Roberts et al.[160] showed an increase in susceptibility to multiple sclerosis in offspring of consanguineous parents. Consanguinity may also have an adverse effect on cognitive performance, which has been shown to be significantly lower in the progeny of consanguineous marriages.[13,26,161-163] Rudan et al. investigated the hypothesis that the heritable component of late onset diseases includes a major class of deleterious recessive alleles. They recently studied the effects of inbreeding on blood pressure among 2,760 adult individuals from 25 villages in a Dalmatian Island isolate. Through this study they observed a large effect of inbreeding on blood pressure equivalent to a rise in systolic blood pressure of ~20 mmHg and diastolic blood pressure of ~12 mmHg in offspring of first cousin marriages.[163]

In another study Rudan et al.[164] extended their observation by investigating the relation between inbreeding and the prevalence of 10 late onset complex diseases of public health importance. The study was conducted in 14 of the original 25 isolate villages on three neighbouring islands in middle Dalmatia, Croatia. These island populations characterized by a wide range of levels of inbreeding and endogamy, reduced genetic variation at both individual and sub-population levels, and relative uniformity of environment. This study indicated the important effect of inbreeding on several genetically complex late onset diseases, that is consistent with the proposal that an important genetic influence on these disorders is mediated by numerous deleterious recessive alleles, suggesting that inbreeding increases disease risk as a result of increased homozygosity.[165]

Further controlled studies in populations with high consanguinity rates are warranted.

CONCLUSION

The study of the impact of consanguinity on bio-viability, be it on fertility, fetal wastage, neonatal morbidity and mortality, or predisposition to a variety of early childhood genetic malformations and syndromes, early complex multifactorial diseases or later-in-life susceptibility to common adult diseases, provides a unique opportunity to begin to challenge our common assumptions about disease and its cure.

It touches the very essence of who we are as humans, where our existence occurs at the nexus of our biology, evolution, culture, traditions and families.

The challenge of the future, after the mapping of the human Genome, is to harness genetics in the service of prevention and cure in the ultimate form of tailored medicine, for the sake of the patient's and society's welfare and medical well-being.

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