

# The Effect of Consanguinity on Neonatal Outcomes and Health

Hussein A. Abbas<sup>a,b</sup> Khalid Yunis<sup>b</sup>

<sup>a</sup>School of Medicine, American University of Beirut, and <sup>b</sup>Department of Pediatrics and Adolescent Medicine, American University of Beirut Medical Center, Beirut, Lebanon

## Key Words

Consanguinity · Preterm birth · Anthropometric measurements · Neonatal mortality · Congenital defects

## Abstract

Consanguineous marriages constitute a significant fraction of marriages worldwide and confer a major public health concern on newborns. In addition to the risk of acquiring a recessive genetic disease, the offspring of consanguineous parents are plausibly at an increased risk of preterm birth, decreased anthropometric measurements, congenital defects and mortality. How consanguinity confers such an increased risk is still largely unknown. In this review, we discuss the effect of consanguinity on selected gestational outcomes by delineating the different studies that have led to such findings. We also investigate the different conclusions that have emerged regarding the effect of consanguinity on gestational outcomes.

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## Introduction

Consanguineous marriages, the unions between blood-related individuals with a common ancestor, are still surprisingly prevalent in certain regions of the world. The impact of consanguinity on selected neonatal outcomes is a public health concern and will be discussed in

this review. Remarkably, almost 10.4% of marriages worldwide are between biological relatives [1]. The attitude towards consanguineous marriages varies significantly among different cultures [2]. Historically, it was only after the 9th century that the Catholic Church started implementing laws forbidding consanguinity, depending on the degree of the kin relationship. With the exception of the USA, North Korea and the People's Republic of China, first-cousin marriages are legal throughout the world [3]. Nowadays, consanguinity is rare in Western culture but more common in Islamic countries as well as in certain tribal or closed communities. Specifically, 20–50% of all marriages among Muslims and Arabs are consanguineous [4, 5]. Also, most kin marriages are between first-degree cousins who share >12% of each other's genes [3, 6]. On the other hand, approximately 1% of marriages are consanguineous in Western Europe, Russia and North America [4, 7].

The underlying factors that promote consanguineous marriages are primarily of a religious, cultural, traditional and/or financial nature [8]. For instance, marriage between blood-related couples strengthens family ties, reduces dowry, maintains family property, and, supposedly, produces more compatible and successful marriages [5, 9]. Consanguinity is more common among families of low socioeconomic status, with a younger age at motherhood, lower literacy, and those who reside in rural areas [6, 10].

Most studies on consanguinity have focused on genetically inherited diseases since the progeny of a consan-

guineous marriage is at a 2-fold greater risk of having an autosomal recessive disorder compared to that of a non-consanguineous marriage [10]. The effects of consanguinity on maternal gestational health and the adverse risk of pregnancy outcomes have emerged and pose a major public health concern. This review summarizes the effects of consanguinity on gestational outcomes, specifically preterm birth (PTB), anthropometric measurements and mortality.

### PTB in Consanguineous Marriages

PTB is defined as birth before 37 weeks of gestation. While global efforts are invested into decreasing neonatal deaths, the offspring of preterm delivery constitute the leading cause of neonatal mortality [11]. The underlying effectors of PTB are still not fully delineated. However, ample evidence suggests that spontaneous PTB can result from the interplay between genetic and multiple environmental risk factors [12]. The effect of consanguinity on gestational age has been a point of debate since the 1950s [13]. Examining the correlation between consanguinity and PTB can provide ample data for our understanding of the genetic components leading to preterm delivery.

One of the initial studies assessing the effect of consanguinity on PTB was conducted on a Japanese population by Morton in 1958 [13]. Gestational length did not differ between unrelated or related couples, irrespective of the degree of kinship. In Saudi Arabia, where consanguinity is a common practice and rates have been consistently high, Saedi-Wong and al-Frayh examined 4,497 pregnancies of couples with a consanguinity rate of 54.3% [14]. In their study, PTB was also not increased among consanguineous marriages. Similar findings of a lack of correlation between consanguinity and PTB were also noted in India and Turkey [15–17]. However, in these studies the authors did not distinguish between spontaneous and medically induced PTB, and the sample sizes were relatively small. Moreover, these studies used 37 weeks as a cutoff point for PTB, without further categorizing it into very PTB ( $\leq 32$  weeks of gestation) or PTB ( $< 37$  weeks of gestation).

Other studies on 236 Saudi [18] and 848 Norwegian women [19] revealed that consanguinity poses an increased risk of PTB at  $< 37$  weeks of gestation. These findings initiated further interest and led to investigations on larger sample sizes for stronger power analyses in different populations. In 2010, 2 larger studies from Jordan [20] and Lebanon [21] emerged and correlated consan-

guinity with PTB. Among 3,269 Jordanian women with a 49% consanguinity rate, inbreeding increased the risk of spontaneous preterm delivery at  $< 37$  weeks of gestation (OR = 1.5; 95% CI, 1.2–1.9) [20]. In a larger cohort of 39,745 Lebanese singleton live births without major birth defects, Mumtaz et al. [21] identified a 1.6-fold increased risk of early spontaneous preterm delivery at  $< 33$  weeks of gestation among consanguineous marriages compared to unrelated parents (OR = 1.6; 95% CI, 1.1–2.4). On the other hand, late PTB or medically indicated PTB were not associated with consanguinity [21]. Notably, an earlier study by Khlaf [22] in a single medical center in Lebanon among 1,252 newborns did not reveal a statistically significant correlation between PTB and consanguinity. However, as with the previously mentioned data from Turkey, India and Japan, this study did not differentiate between spontaneous and medically indicated PTB.

As discussed earlier, the components contributing to PTB are still not fully known and further research is warranted. So, how does consanguinity contribute to PTB? Several studies suggest that heritable genetic components, largely from the maternal side, plausibly dictate the gestational age. In a Norwegian study, maternal and fetal genetics contributed to the gestational age variation by 14% and 11%, respectively [23]. Also, in another study, each additional week of the mother's gestational age prolonged the gestational age of the child by 1.22 days [24]. Among family members, there is a 1.6–1.8-fold increased risk for sisters – but not brothers – of women who had PTB to have preterm delivery themselves, further corroborating the evidence of a strong maternal contribution [25–27]. Also, the recurrence of PTB suggests an underlying genetic component influencing pregnancy outcomes (OR = 5.6; 95% CI, 5.5–5.8) [26]. These findings strongly support the hypothesis that specific genes are responsible for ‘calibrating’ the gestational age. However, the paternal genetic component for preterm delivery has not been found to be significant, although further studies are required to prove this notion [25, 26]. It would be interesting to assess PTB in women who conceived pregnancies with two different partners to further assess the role of maternal genetics on preterm delivery.

### Anthropometric Measurements in Newborns of Consanguineous Parents

While only few studies have addressed the role of consanguinity in preterm delivery, more research has investigated the variation of anthropometric measurements as

a result of consanguineous marriages. Anthropometric measurements are highly influenced by maternal nutrition, the socioeconomic status, gestational complications such as hypertension and diabetes, maternal gestational weight gain, and the maternal pre-pregnancy body mass index. Most of the analyses in published reports focus on birth weight and length of the baby, and the conclusions vary depending on the population under study and the research design. Significantly, birth weight is one of the strongest predictors of neonatal mortality and morbidities in the newborn and young infant stages [28]. Hence, any preventable factors that negatively affect birth weight should be avoided to improve the survival rate of newborns, especially in the light of non-modifiable conditions such as gender.

In 1980, Rao and Inbaraj [15] showed that in 20,000 pregnancies in India there were no differences in anthropometric measures between consanguineous and non-consanguineous marriages. Similarly, studies on Pakistani Muslims and from Saudi Arabia, Turkey, and Japan did not find a correlation between consanguinity and birth weight changes [13, 14, 16, 29]. However, maternal nutrition was not controlled in these studies. It is possible that the high prevalence of malnutrition among women in India and Pakistan has influenced the anthropometric measurements of their offspring irrespective of consanguinity.

On the other hand, recent studies from Pakistan and Jordan identified consanguinity as a risk factor for small-for-gestational-age babies [20, 30]. In Lebanon [22], one study failed to show a significant pattern of weight, length, and head and chest circumference of newborns correlated with consanguinity. However, a more recent and larger Lebanon-based study [31] by our group has reached a different conclusion. In this study, after controlling for sociodemographic and medical covariates, consanguinity significantly decreased birth weight for gestational age by 1.8% [31]. Other studies on populations from Israel, Qatar, and Saudi Arabia also showed a significant decrease of birth weight in consanguineous marriages [32–35]. Interestingly, the studies on the Lebanese and Jordanian populations that showed an influence of consanguinity on PTB also correlated consanguinity with decreased birth weight [20, 21, 31]. On the other hand, several of the previously discussed studies that did not find a correlation between consanguinity and PTB also failed to show a correlation with decreased birth weight. This observation requires further scrutiny about confounding factors with consanguinity that may lead to both PTB and decreased birth weight.

## Mortality in Neonates of Consanguineous Marriages

Neonatal mortality is affected by a plethora of genetic, environmental, and maternal factors. For instance, it is well established that maternal age, birth spacing (i.e. increasing the time between pregnancies), and a history of previous losses are risk factors for neonatal mortality [36]. PTB is the leading factor associated with neonatal mortality. Several studies aimed to address whether consanguinity increased the risk of neonatal mortality and stillbirth. Surprisingly, very few studies investigated whether the offspring of consanguineous parents may have different Apgar scores and fetal distress compared to the offspring of non-consanguineous parents.

In 1990, Wong and Anokute [37] conducted the first study in Saudi Arabia to investigate the birth outcomes of consanguineous pregnancies. Spontaneous abortions, induced abortions and stillbirths were higher among consanguineous marriages [37]. Also, 57.9%, 60.3% and 62% of neonatal, infant and perinatal deaths, respectively, occurred in consanguineous marriages [37]. Among consanguineous unions, first-cousin marriages consistently had a higher frequency of mortality compared to a more distant relatedness, further supporting the evidence of the effect of underlying consanguineous genetics on neonatal outcomes [37]. On the other hand, a Kuwaiti study [38] did not show a significant difference in prenatal and neonatal mortality between consanguineous and non-consanguineous marriages. A study by Barbour and Salameh [39] in Lebanon did not find a correlation between consanguinity and offspring mortality, although consanguinity was associated with spontaneous miscarriages and childhood chronic morbidities (OR = 1–2). A study from Oman [9], however, promoted the public acceptance of consanguineous marriages as the author did not find a significant effect of consanguinity on fertility or offspring mortality.

According to the Pakistan Demographic and Health Survey [36], more than 60% of marriages in Pakistan are consanguineous, which provides an excellent resource to understand the effect of consanguinity on neonatal health. In a Pakistani study, perinatal mortality was 2-fold higher among consanguineous parents (95% CI, 1.5–2.6), even after controlling for biological and sociodemographic factors [36]. In fact, after the appropriate adjustments, consanguinity with inbreeding (i.e. where one or both of the offspring's parents are the product of consanguinity themselves) exerted a stronger risk for perinatal loss than consanguinity without inbreeding, in both a Pakistani study [36] and one based on 12 generations of the Amish

community [40]. Several other studies corroborate the evidence that parental consanguinity is a major contributory factor to mortality in the neonatal, postnatal, infant and under 5-year-old groups [19, 32, 41, 42]. In fact, our group also showed that consanguinity is an independent risk factor for in-hospital neonatal deaths [43]. In a study on more than 140,000 Palestinian live births in the Middle East, Pedersen [44] showed that there was an increase of 15 additional deaths per 1,000 births among babies of first cousins. Interestingly, this correlation still held true, but to a lesser extent, among married couples from the same patrilineal clan [44].

The different conclusions drawn on the effect of consanguinity on offspring mortality can be attributed to the research design of each study and the lack of proper adjustments for non-genetic variables. Since consanguinity increases the risk of inheriting 2 lethal recessive alleles, the cause of death could be due to rare recessive genetic diseases which cannot be accounted for rather than due to an effect of consanguinity per se. Also, only a few studies have reported on congenital malformations that may have led to neonatal deaths. This variable is not usually adjusted for.

While consanguinity may have an adverse effect on neonatal mortality, the general belief is that it may have a greater impact on the infant and juvenile life of the offspring [45]. To that end, it would be interesting to have a long-term follow-up of infants born to consanguineous parents in a case-control analysis.

### Other Complications

Studies have also been conducted on correlating consanguinity with fertility, stillbirths, apnea in the premature newborn, and abortion [13, 20, 46]. The conclusions regarding these correlations varied among different populations, the time of the study, and research groups. It is generally agreed that the rates of birth defects are higher in the offspring of consanguineous parents and can result in severe disabilities and an increased mortality rate [10]. For instance, first-cousin marriage offspring are at a significantly increased risk of congenital heart disease, and almost 40% of Saudi children with heart defects are the children of first-cousin marriages [47]. Additionally, spina bifida, epilepsy, hydrocephalus, cleft lip or palate, and congenital deafness are more common in consanguineous offspring [48–53].

In addition to organic diseases, consanguinity significantly increases the risk of intellectual disability, as shown

in a Bangladeshi study [54]. In a Pakistani population [55], this was not observed, although both studies were conducted by the same group of researchers and had similar designs. The variation in these results further corroborates the assumption that the extent of adverse effects caused by consanguinity may be multifactorial in nature. In addition, hyperactivity, learning and reading disorders are significantly more common among consanguineous unions [56–58].

### Conclusions

This paper reviewed the correlations between consanguinity and PTB, birth weight and length, mortality, and congenital defects. The results regarding the correlation of consanguinity with PTB, birth weight and length and neonatal mortality are not consistent among various studies. This variability is attributable to population sizes, sociodemographics, research design and inadequate adjustment for confounding factors. For instance, most studies analyzing the risk of PTB with consanguinity did not differentiate spontaneous from medically induced PTB. As for birth weight and length, nutrition is an important modifying factor that none of the studies have controlled for. A larger consensus, however, has been reached with regard to the effect of consanguinity on congenital disease, and specifically congenital heart defects such as univentricular morphology and ventricular or atrial septal defects. With the increasing evidence of complications and adverse outcomes resulting from consanguineous pregnancies, public health awareness programs should be initiated by the health authorities in regions of high consanguinity in order to decrease the potential risk of gestational problems, adverse health effects, congenital defects and psychiatric alterations. Further, the consanguinity study group that convened in Geneva in 2010 highlighted the importance of counseling and genomic and social research to identify the outcomes associated with consanguinity [59]. In addition to decreasing morbidity, awareness of the effects of consanguinity on offspring may also contribute to a decrease in neonatal mortality.

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