1-1-2015

Consanguinity and pregnancy outcomes in a multi-ethnic, metropolitan European population

Rolf Becker

Thomas Keller

Rolf-Dieter Wegner

Heidemarie Neitzel

Markus Stumm

See next page for additional authors

10.1002/pd.4487

This is the peer reviewed version of the following article: [Becker R., Keller T., Wegner R.-D., Neitzel H., Stumm M., Knoll U., Stark M., Fangerau H., & Bittles A. (2015). Consanguinity and pregnancy outcomes in a multi-ethnic, metropolitan European population. Prenatal Diagnosis, 35(1), 81-89], which has been published in final form here. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

This Journal Article is posted at Research Online.

https://ro.ecu.edu.au/ecuworkspost2013/313

PRENATAL DIAGNOSIS
ispd International Society for Prenatal Diagnosis

Consanguinity and pregnancy outcomes in a multi-ethnic, metropolitan European population

Journal:	*Prenatal Diagnosis*
Manuscript ID:	PD-14-0233.R1
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Becker, Rolf; Center for prenatal diagnostics and human genetics, prenatal diagnostics Keller, Thomas; Acomed Statistics, Wegner, Rolf-Dieter; Center for Prenatal Diagnosis and Human Genetics, Neitzel, Heidemarie; Charité-Universitätsmedizin Berlin, Department of Medical and Human Genetics Stumm, Markus; Center for Prenatal Diagnosis and Human Genetics, Knoll, Ute; Center for Prenatal Diagnosis and Human Genetics, Staerk, Markus; Center for Prenatal Diagnosis and Human Genetics, Fangerau, Heiner; Institute of the History, Theory and Ethics of Medicine, Bittles, Alan; Edith Cowan University, School of Medical Sciences
KeyWords:	Fetal ultrasound < FETAL IMAGING, Array CGH < PRENATAL CYTOGENETICS, General cytogenetics < PRENATAL CYTOGENETICS, SINGLE GENE DISORDERS, Consanguinity, ethnicity

Consanguinity and pregnancy outcomes in a multi-ethnic, metropolitan European population

Running head: Consanguinity and prenatal health

Rolf Becker[1*], Thomas Keller[2], Rolf-Dieter Wegner[1], Heidemarie Neitzel[3], Markus Stumm[1], Ute Knoll[1], Markus Stärk[1], Heiner Fangerau[4] and Alan Bittles[5,6]

[1]Center for Prenatal Diagnosis and Human Genetics, Berlin, Germany
[2]Acomed Statistics, Leipzig, Germany
[3]Department of Medical and Human Genetics, Charité-Universitätsmedizin Berlin, Berlin, Germany,
[4]Institute of the History, Theory and Ethics of Medicine, University of Ulm, Ulm, Germany
[5]Centre for Comparative Genomics, Murdoch University, Perth, Australia
[6]School of Medical Sciences, Edith Cowan University, Perth, Australia

[*]Correspondence to: Rolf Becker. E-mail: bedaktari@t-online.de

Funding sources: none
Conflicts of interest: none

CORRESPONDENCE:

Prof. Dr. Rolf Becker
Center for Prenatal Diagnosis and Human Genetics
Kurfürstendamm 199
D-10719 Berlin
GERMANY
Tel: +49-30-88043166
FAX: +49-30-882 56 06
E-mail: bedaktari@t-online.de

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

Numerous studies of postnatal cohorts show that consanguineous couples have an increased risk of major anomalies in their offspring. Up to now, no comprehensive study exists showing that the risk of major congenital anomalies in the offspring of consanguineous couples is higher than previously estimated if the prenatal situation is included

WHAT DOES THIS STUDY ADD?

Adjusted frequencies of major anomalies were 2.8% in non-consanguineous,6.1% in consanguineous couples (8.5% in first cousin progeny, 3.9% in beyond first cousin). Applying a further adjustment for the significantly different frequencies of trisomic pregnancies (consanguineous: n = 1, non-consanguineous: n = 262), the overall risks were 2.0% and 5.9% respectively, i.e. a 3.9% excess risk attributable to consanguinity, 6.1% at first cousin level , 1.9% beyond first cousin level.

Statement: Originality of publication

The paper is submitted nowhere else.

Statement: Ethics

The data are anonymized retrospective evaluations of normal clinical treatment. Institutional or national ethical committee approval is therefore not required.

OBJECTIVE: Aim of the present study was to assess the risk of major anomalies in the offspring of consanguineous couples, including data of the prenatal situation.

METHODS: Over 20 years (1993-2012), 35,391 fetuses were examined by prenatal sonography. In 675 cases (1.9%) parents were consanguineous, with 307 couples (45.5%) related as first cousins, 368 couples (54.5%) beyond first cousins,. Detailed information was retrieved on 31,710 (89.6%) fetuses, (consanguineous 568: 1.8%).

RESULTS: Overall prevalence of major anomalies among fetuses with non-consanguineous parents was 2.9% (consanguineous: 10.9%: first cousins 12.4%, beyond first cousins 6.5%). Adjusting the overall numbers for cases having been referred because of a previous index case, the prevalences were 2.8% (non-consanguineous) and 6.1% (consanguineous) (first cousin 8.5%, beyond first cousin 3.9%). Further adjustment for differential rates of trisomic pregnancies indicated 2.0%/5.9% congenital anomalies (non-consanguineous/consanguineous groups), i.e. a consanguinity-associated excess of 3.9%, 6.1% in first cousin progeny and 1.9% beyond first cousin.

CONCLUSIONS: The prevalence of major fetal anomalies associated with consanguinity is higher than in evaluations based only on postnatal life. It is important that this information is made available in genetic counselling programmes, especially in multi-ethnic and multi-religious communities, to enable couples to make informed decisions.

Introduction

Marriages between couples related as second cousins or closer are common in many societies and it is estimated that at least 10.4% of the current world population of 7.2 billion people are consanguineous, with first cousin marriages by far the most prevalent type of intra-familial union.[1-3] The frequency of consanguineous marriage is especially high in South, Central and West Asia, and in North and sub-Saharan Africa[2], and in countries such as Pakistan first cousin marriages alone account for >50% of all marital unions.[4] Given the presence of large Asian and African immigrant communities in Europe, North America, and Oceania[5-14], consanguineous pregnancies are now routinely encountered in many antenatal clinics in Western countries, which has resulted in heightened interest in the possible association between consanguinity and adverse pregnancy outcomes.

Data from epidemiological studies evaluating health outcomes have consistently shown that the offspring of consanguineous parents may be at increased risk of morbidity and death in the first years of life, due to the expression of detrimental recessive genes co-inherited from a common ancestor.[1,3,15-19] A recent multi-population meta-analysis indicated a mean excess infant death rate of 1.3% in the progeny of first cousins, with a total excess pre-reproductive mortality at first cousin level of 3.7%.[2] When compared with non-consanguineous offspring, first cousin progeny had a 4.4% mean excess risk of a major congenital defect (median excess risk = 3.3%).[2]

To date, information on the effects of consanguinity on fetal well-being have been very limited, with few representative data available on fetal losses or on the prevalence of major congenital anomalies. Since a proportion of pregnancies with major anomalies may end in intrauterine death, or in medical termination, estimates of fetal defects based only on postnatal data may be misleading. The present detailed study was therefore undertaken to provide information on two important topics:

1) The frequency of fetuses with consanguineous parentage in a major European metropolitan population;

2) The comparative frequency of major anomalies resulting in intrauterine or neonatal death (IUD/NND), medical termination of pregnancy (MTOP), and neonatal survival in the offspring of consanguineous and non-consanguineous parents.

Patients and Methods

The study was based on sonographic examinations (some undertaken in combination with sonographically guided invasive procedures) conducted in a specialist reference centre in Berlin, the capital of Germany over a 20-year period (January 2, 1993 to December 30, 2012). A total of 35,391 fetuses in 34,256 pregnancies with a gestational age of more than 10 weeks underwent prenatal examination, including 953 sets of twins, 73 sets of triplets and 12 sets of quadruplets.

Various reasons for referral were given, including a positive family history; suspicion of a malformation raised by a referring colleague; problems in sonographic depiction, for example, because of maternal obesity; or concern of the pregnant woman with regard to possible fetal anomalies and her wish, and that of the referring physician, to exclude fetal anomalies wherever possible. However, in the latter instance the German legal guidelines on pregnancy surveillance curtail the right of a woman to be referred for a detailed scan only where there is suspicion of an anomaly.

All ultrasound examinations were performed by a single operator (RB), and the sonographic instruments used were, respectively, an Acuson 128XP10, a Siemens Acuson Sequoia, and a GE Voluson E8. In addition to the ultrasound examinations, patients' histories were assessed by questionnaires as well as personal interviews.

The ultrasound examinations were conducted between 10+0 and 42+0 weeks gestation (median 21+2 weeks), with 11,108 fetuses examined between 10+0 and 13+6 weeks, i.e. at the first trimester anomaly scan, and 16,814 fetuses examined between 20+0 and 23+6 weeks, i.e. at the second trimester anomaly scan. A total of 4,771 fetuses were examined between 14+0 and 19+6 weeks and 2,698 fetuses between 24+0 and 41+3 weeks. According to the German system of perinatal care, all newborns were examined by a midwife

immediately after birth and by a paediatrician between days five and ten of life. Reports on the health status of the newborns, either provided by mothers or in medical reports, were based on the results of these mandatory examinations. A major anomaly was defined as a defect present during pregnancy after 10 weeks gestation that, in the absence of treatment, either was incompatible with life or would lead to a severe handicap and would be detectable during the paediatric examination at five to 10 postnatal days.[20,21]

As part of a standardized form distributed during the explanatory talk preceding ultrasound examination, each patient was asked during the first prenatal interview whether she and her partner were biological relatives, and if so the nature of their relationship, i.e. categorized as first cousin, equivalent to a coefficient of inbreeding, $F = 0.0625$, or related to a lesser degree, $F<0.0625$. All patients also were requested to complete and return a feedback form after delivery, containing information on their pregnancy, the birth, and the health of their newborn.

Feedback on the fetal outcome was retrieved for 31,710 (89.6%) of the 35,391 cases, representing 568/675 (84.1%) of the consanguineous and 31,141/34,716 (89.7%) of the non-consanguineous cases respectively (Table 2). In 15,730 cases (consanguineous, n = 191) the form was returned by the patient, and in 15,411 cases (consanguineous, n = 377) by contacting the patient or, especially in cases with an adverse pregnancy outcome, via the referring physician or the hospital where the child had been delivered or the pregnancy had been terminated. The information on the health status of the fetus/newborn contained all ultrasound results during the pregnancy as well as post-partum information retrieved by the second routine examination of the newborn performed between day 5 and 10 of neonatal life.

A majority of the ultrasound examinations was undertaken for screening purposes.

In patients with a congenital anomaly, the frequency referred because of the medical history of an index child with an autosomal recessive disorder in the consanguineous group was much higher (29 of 62: 46,8%) than in the non-consanguineous group (10 of 893: 1.1%) (Table 3, Suppl. Table 5)..

Data on ethnicity and maternal age were available for all 675 consanguineous cases and for 34,526 (99.5%) of the non-consanguineous fetuses (Table 1). Patients were classified into five major groups:

1. European, predominantly German, but also parents from other European countries and of European ancestry, including North and South America, Russia and Australia;

2. Turkish, i.e. parents from Turkey, which may include parents of Kurdish ethnicity;

3. Eastern Mediterranean, i.e. from Iran, Iraq, Israel, Kuwait, Lebanon, Oman, Palestine, Syria, Saudi Arabia, and Yemen; also Egypt and the Maghreb states Algeria, Libya, Morocco, Tunisia, as well as Pakistan and Sudan;

4. African, mainly sub-Saharan, and

5. South, Southeast and East Asian, i.e. Bangladesh, China, India, Indonesia, Nepal, The Philippines.

The data on an association between consanguinity and a major fetal anomaly were divided into three categories A causative association between consanguinity and fetal or neonatal disease was assessed as:

1. ***Probable:*** if i) the disease was rare and had a well described autosomal recessive mode of inheritance, and/or, ii) there were several identical anomalies affecting fetuses previously conceived by a woman (or in the pregnancies of close biological relatives), with a suspected but as yet unproven autosomal recessive mode of inheritance;

2. ***Possible:*** in cases of anomalies that may occur as autosomal recessive diseases but where the mode of inheritance was unclear and no repeat case was known;

3. ***Improbable:*** in cases known not to have an autosomal recessive mode of inheritance, and in cases with numerical or structural chromosomal abnormalities.

Statistical analysis

The statistical analysis was performed using the SAS®9.2 program (SAS Institute Inc., Cary, North Carolina, USA). Summary statistics are presented as counts and percentages in the case of categorically scaled measures and as mean, median, standard deviation and range in the case of continuously scaled variables, with the fetus or the mother as the unit of analysis.

Multivariable Poisson regression was undertaken to investigate the effect of consanguinity on the occurrence of anomalies, with the analysis adjusted for maternal age, ethnicity and the birth number (1st pregnancy: y/n). The latter adjustment was performed in order to address a possible referral bias. Pregnancy was the unit within these analyses; in the case of multiple pregnancies the fetus with worst birth outcome was used in the analysis. As a further sensitivity analysis to address missing information on fetal outcome, the Poisson regression was repeated by applying multiple imputation[22] of missing information (SAS procedures PROC MI, PROC MIANALYZE, 20 imputation cycles), under the assumption that missing outcome information (MAR) could be explained by consanguinity, ethnicity, maternal age and first pregnancy y/n ("missing at random assumption" (MAR)[23)].

Results

Of the total 35,391 fetuses examined 676 (1.9%) were the offspring of consanguineous parents. In one of these cases the pregnancy was conceived by egg donation and so it was categorized as genetically non-consanguineous, resulting in 675 fetuses conceived by consanguineous parents (Table 1). Within this group, the parents of 307/675 (45.5%) fetuses were first cousins, with an established outcome in 275 cases; the parents of 368/675 (54.5%) fetuses were related beyond first cousin, with an established outcome in 293 cases.

The frequency of parental consanguinity varied significantly according to the ethnicity of the mothers, from just 0.07% in European, predominantly German couples, to 21.8% consanguinity in couples of Eastern Mediterranean/Maghreb ethnicity who formed 33.6% of the total consanguinity group, and 17.2% in women of Turkish origin who comprised 61.5% of all consanguineous cases (Table 1).

The overall frequency of major anomalies was 893/31,141 (2.9%) in the non-consanguineous group, 22 of them with a well known autosomal-recessive background (Table 3, Suppl. Table 5). In the consanguineous group, the frequency of major anomalies was 62/568 (10.9%). As previously noted, in the consanguineous group 29/62 cases had been referred because of a preceding index case, by comparison with 10/893 non-consanguineous cases (Suppl. Table

5). Adjusting for the pregnancies with preceding index cases and analysing in terms of the level of parental consanguinity the percentages of congenital anomalies diagnosed were: all consanguineous 6.1% (33 of 539), first cousin 8.5% (22 of 259), beyond first cousin 3.9% (11 of 280), and non-consanguineous 2.8% (883 of 31,131) (Tables 2, 3).

The frequency of anatomically complex diseases also was higher in the total consanguineous (3.7%) than in the non-consanguineous (1.5%) group. Conversely, while 0.7% of the consanguineous group was diagnosed with chromosomal anomalies with 177 cases of trisomy 21, 56 cases of trisomy 18 and 29 cases of trisomy 13., the prevalence of chromosomal anomalies in the non-consanguineous group was 1.2% (Table 2) with 1 case of trisomy 21 and no cases of trisomy 13 or 18.

Additional investigative procedures, including chorionic villous sampling, amniocentesis and fetal blood sampling, were less frequently undertaken in the pregnancies of women in a consanguineous relationship (7.0%) than non-consanguineous women (11.7%). A similar pattern emerged in the cases where a major anomaly was suspected, with 14.5% of consanguineous cases as opposed to 30.7% of non-consanguineous pregnancies further investigated (Suppl. Table 1).

Detailed information on the 62 cases of major anomalies considered to be probably, possibly, or improbably associated with parental consanguinity is presented in Tables 3 and 4. In cases 1-37 (59.7%), 21 of whom had first cousin parents and 16 with parents related beyond first cousins, a causal relationship of the disease with consanguinity was assessed as probable, e.g. glycogenosis or SMA Werdnig-Hoffmann (Table 3). In cases 38-56 (30.6%), 11 of whom had first cousin parents and 8 with parents related beyond first cousins, an association between the major anomaly and consanguinity was possible but could not be proven, e.g. hydrops of unknown aetiology (Table 4). In cases 57-62 (9.7%), all of whose parents were first cousins, there was no obvious association between the major anomaly and parental consanguinity, e.g. Klinefelter syndrome (Table 4). In 10/37 cases listed in Table 3 a diagnosis was possible by molecular diagnostics following an invasive procedure; in 3 further

cases of this group diagnosis would have been possible but was declined by the pregnant woman.

Intra-uterine death occurred in 9.7% of the consanguineous fetuses versus 4.9% of the non-consanguineous pregnancies, and the corresponding data on medical terminations of pregnancy were 50.0% and 60.9% respectively. Nine of 62 (14.5%) fetuses of consanguineous progeny with major anomalies died within the first year of life, 3 within the first week. Detailed information on the time and mode of detection as well as time and mode of the demise (unless the newborn survived) of the fetus/newborn are given in columns 6 and 9 of table 3 and columns 5 and 8 of table 4.

The results of adjusted, multivariable analyses (without and with multiple imputation of missing information) are presented as Supplementary Results. A ratio of abnormalities Cons/P/NConsP of 3.00 (95% CI: 2.17 – 4.14) [multiple imputation: 3.00 (95% CI= 2.15 – 4.19)] was found. In the preparation of multiple imputation, all investigated variables were identified as explanatory variables for missing information of outcome (Suppl. Table 1).

Discussion

To the best of our knowledge this is the first comprehensive study analysing the impact of consanguinity on the frequency of congenital anomalies which includes comprehensive data on prenatal life from week 10 onwards. Besides the integration of prenatal data, a major advantage of the evaluation is the size of the study group which gives a representative picture of the diagnostic situation faced.

The overall frequency of fetuses with consanguineous parentage in our study population was low (1.9%) in comparison to the many countries where 20-50+% of all marriages are consanguineous (www.consang.net).[2,3] Consanguinity was strongly associated with ethnicity: consanguineous relationships were most common among couples of Turkish or Eastern Mediterranean/Maghreb origin, with 95.1% of all consanguineous fetuses studied conceived by couples from these backgrounds.

The investigation was based on retrospective data gained as part of the daily routine of a specialist prenatal practice over 20 years. When such observational data are analysed possible biases influencing the result have to be considered. First, one could assume that the women undergoing prenatal diagnosis following their first pregnancy might differ from those women who visited the practice during their first pregnancy (1st pregnancy y/n). We therefore undertook a multivariable analysis investigating the effect of consanguinity on the occurrence of anomalies and adjusted the analysis for this factor (together with age and ethnicity). The related IDR (1st pregnancy y/n) was 1.03 (95%-CI: 0.90 - 1.19, p = 0.62), indicating that such bias was negligible (Suppl. Table 1). Second, the feedback rate of pregnancies was lower in the consanguineous (84.1%) than in the non-consanguineous (89.6%) group, which might also influence the result. We therefore used multiple imputation[22], assuming that the rate of missing information on the occurrence of an anomaly can completely be explained by variables (consanguinity, age, ethnicity, first pregnancy (y/n)) investigated in the study (MAR assumption).[23] Although all variables could potentially influence the rate of missing information, the overall result was almost identical: (MI analysis: IDR (cons y/n) = 3.00

279 (95%-CI: 2.15 - 4.19, p<0.0001) vs. complete case analysis: 3.00 (95%CI: 2.17 -
280 4.14, p = 0.0001) (Suppl. Table 1).
281 The analysis thus shows that with respect to these possible variables the original analysis of
282 10.9% vs. 2.9% (ratio 3.8) congenital anomalies in the consanguineous and non-
283 consanguineous groups moderately overestimated the apparent influence of consanguinity on
284 the occurrence of anomalies, i.e. consanguinity significantly influences the occurrence of
285 anomalies independently of other factors. It therefore is appropriate to present further detailed
286 analyses simply as counts and percentages.
287 In overall terms, Table 3 lists 8 cases with a congenital anomaly probably associated with
288 consanguinity because of an established autosomal recessive inheritance but without a
289 preceding index child. Table 4 lists 19 cases possibly related to consanguinity and 6 cases
290 probably not related to consanguinity.
291 The degree of consanguinity had important influence on the frequency of major anomalies:
292 looking at all consanguineous cases, the frequency of 6.1% could be differentiated into a
293 subgroup of first cousin relations with a frequency of major anomalies of 8.5% and a
294 subgroup beyond first cousin with a frequency of 3.9% respectively.
295 Having adjusted for previously diagnosed index cases and assuming similar background risks
296 in the consanguineous and non-consanguineous cases, congenital anomaly rates of 33/539
297 (6.1%) and 883/31,131 (2.8%) are indicated in the cases with consanguineous and non-
298 consanguineous parentage respectively.
299 Consanguineous women were, however, significantly younger than non-consanguineous
300 women (Table 1) resulting in a differential age-dependent frequency of trisomies. In the non-
301 consanguineous group there were 262 trisomy cases (T21: n = 177; T18: n = 56; T13: n =
302 29), i.e. a frequency of 262/893 (29.3%) major anomalies. As previously noted, this group of
303 non-consanguineous fetuses also comprised 22 cases with an established autosomal recessive
304 mode of inheritance (Suppl. Table 5), 10 of whom had a preceding index case.
305 The background frequency of the non-consanguineous group corrected for autosomal
306 recessive cases with a preceding index case and trisomies results in an adjusted frequency of

[(893-10-262)/(31,141-10-262)] = 2.0%. By comparison, in the consanguineous group, besides the autosomal recessive cases with a preceding index patient there was a single case of trisomy 21 resulting in an adjusted major anomaly frequency of [(62-29–1)/(568-29-1)] = 5.9%. The overall excess consanguinity-associated prevalence of congenital anomalies in the combined offspring of first cousin and beyond first cousin parents is therefore 5.9%-2.0% = 3.9%: 6.1% (100x(22-1/275-1-16)% –2%) at first cousin level and 1.9% (100x(11/293-13)%-2%) beyond first cousin level. By comparison, meta-analyses of multi-national data have indicated a 0.5% increase in stillbirths and a 1.25% increase in infant deaths among the progeny of first cousin parents[2].

Where the fetus was diagnosed with a major congenital anomaly there was a high prevalence of medical termination of pregnancy in both the consanguineous (50.0%) and non-consanguineous pregnancies (60.9%). The high rate of medical terminations of affected fetuses conceived by consanguineous couples of Turkish or Eastern Mediterranean origin (Tables 3 and 4) appears to indicative of more permissive attitudes towards MTOP within some Islamic communities.[24]

As summarized in Table 5, in assessing the influence of parental consanguinity on congenital anomalies it is important that prenatal outcomes and early neonatal deaths are fully considered, In the study group, 307/955 (32.2%) fetuses with major anomalies survived the first neonatal week, with quite similar survival outcomes in the fetuses of consanguineous (35.5%) and non-consanguineous (31.9%) parentage (Table 5). From the perspective of a paediatrician, possibly unaware of MTOP, IUD or NND of the child within the first week, the frequency of major anomalies in fetuses with consanguineous parentage, including those referred following an index case, would have been estimated as 3.9% (22/568). However this mode of calculation significantly under-estimates the overall fetal (and neonatal) problems that may be associated with consanguineous pregnancies, even in populations where consanguineous marriage is quite rare. Appropriate allowance for the influence of consanguineous parentage becomes all the more important in multi-ethnic populations where

a significant proportion of pregnancies are between close biological kin and/or contracted within restricted community marriage pools.[2,3,25,26]

With the increasing capacity to maintain fetal life from the second trimester onwards, and to rapidly identify rare inherited disorders by methods such as high-level ultrasound[27], whole genome sequencing in the prenatal period[28] and in neonates[29], and diagnostic whole exome sequencing[30], comprehensive pre- and postnatal procedures need to be devised for adverse consanguinity-associated health outcomes.[31] At the same time, it is important that the information derived be incorporated into genetic counselling programmes that both acknowledge and respect the religious and cultural beliefs of couples and their communities, and the perceived social benefits of intra-familial marriage.[3,32,33] The present study impinges on a potentially very sensitive issue and for this reason the data analysis has been conducted with no attempt to draw any form of moral inference from the results. It therefore is important that the information derived is not assessed outside a medical context or used as a basis for cultural or political discourse.

References

1. Bittles AH, Black ML. Consanguinity, human evolution , and complex diseases. Proc Natl Acad Sci USA 2010;107 (Suppl 1):1779-86
2. Bittles AH. Consanguinity in Context, Cambridge University Press, Cambridge 2012:320.
3. Hamamy H, Antonarakis SE, Cavalli-Sforza LL, et al. Consanguineous marriages, pearls and perils: Geneva international consanguinity workshop report. Genet Med 2011;13:841-7
4. Ahmed T, Ali SM, Aliaga A, et al. Pakistan Demographic and Health Survey 1990/91. Pakistan National Institute of Population Studies and Macro International, Islamabad and Columbia, MD 1992
5. Stoltenberg C, Magnus P, Lie RT, et al. Birth defects and parental consanguinity in Norway. Am J of Epidemiol 1997;145:439-48.
6. Nelson J, Smith M, Bittles AH. Consanguineous marriage and its clinical consequences in migrants to Australia. Clin Genet 1997;52:142-6
7. Reniers G. Postmigration Survival of Traditional Marriage Patterns: Consanguineous marriage among Turkish and Moroccan immigrants in Belgium. Interuniversity Papers in Demography, PPD-1 Working Paper 1998-1. Gent: Department of Population Studies, University of Gent 1998
8. Shaw A. Kinship, cultural preference and immigration: Consanguineous marriage among British Pakistanis. J Royal Anthrop Inst 2000;7:315-34
9. Bennett RL, Motulsky AG, Bittles AH, et al. Genetic counseling and screening of consanguineous couples and their offspring: recommendations of the National Society of Genetic Counselors. J Genet Couns 2002;11:97-119.
10. Port KE, Mountain H, Nelson J, Bittles AH. Changing profile of couples seeking genetic counseling for consanguinity in Australia. Am J Med Genet A 2005;132A:159-63

11. De La Torre J, Coll C, Coloma M, et al. Antenatal care in immigrants. An Sist Sanit Navar 2006; 29 Suppl 1: 49-61
12. Waelput AJM, Achterberg PW. Kinderwens van Consanguïne Ouders: Risico's en Erfelijkheidsvoorlichting, RIVM Rapport 270032003/2007. RIVM: Bilthoven 2007
13. Posch A, Springer S, Langer M, et al. Prenatal genetic counseling and consanguinity. Prenat Diag 2012;32:1133-8
14. Sheridan E, Wright J, Small N, et al. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. Lancet 2013;382:1350-9
15. Bundey S, Alam H. A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding. Eur J Hum Genet 1993;1:206-19
16. Jaber L, Halpern GJ, Shohat M. The impact of consanguinity worldwide. Community Genet 1998;1:12-7
17. Bittles AH. Consanguinity and its relevance to clinical genetics. Clin Gen 2001;60:89-98.
18. Shieh JTC, Bittles AH, Hudgins L. Consanguinity and the risk of congenital heart disease. Am J Med Genet Part A 2012; 158A:1236-41
19. Charafeddine L, Ammous F, Kobeissi L, et al. In-hospital neonatal mortality and the role of consanguinity. Paediatr Perinat Epidemiol 2012;26:398-407.
20. Becker R, Wegner RD. Detailed screening for fetal anomalies and cardiac defects at the 11-12-week scan. Ultrasound Obstet Gynecol 2006;27:613-8
21. Becker R, Schmitz L, Kilavuz S, et al. 'Normal' nuchal translucency: a justification to refrain from detailed scan? Analysis of 6858 cases with special reference to ethical aspects. Prenat Diagn 2012;32:550-5
22. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York : Wiley, 1987
23. Rubin DB. Inference and missing data. Biometrika 1976;63:581-92

24. Bittles AH, Hamamy, H. Endogamy and consanguineous marriage in Arab populations. In Genetic Disorders among Arab populations, 2nd ed., A. Teebi, Springer, Heidelberg 2010:85-108.
25. Bittles AH. A Community Genetics perspective on consanguineous marriage. Public Health Genomics 2008;11:324-30.
26. Bittles AH. Consanguineous marriages and congenital anomalies. Lancet 2013;382:1316-7.
27. Søgaard M, Vedsted-Jakobsen A. Consanguinity and congenital abnormalities. Ugeskr Laeger 2003;165:1851-5
28. Talkowski ME, Ordulu Z, Pillalamarri V, et al. Clinical diagnosis by whole-genome sequencing of a prenatal sample. New Engl J Med 2012;367:2226-32
29. Saunders CJ, Miller NA, Soden SE, et al. Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. Sci Transl Med 2012;4,154ra135.
30. Yang Y, Muzny DM, Reid JG, et al. Clinical whole exome-sequencing for the diagnosis of Mendelian disorders. New Engl J Med 2013;369,1502-11
31. Romeo G, Bittles AH. Consanguinity in the contemporary world. Hum Hered;77,6-9.,
32. Al Aqeel AI. Islamic ethical framework for research into and prevention of genetic diseases. Nat Genet 2007;39:1293-8
33. Bhopal RS, Petherwick ES, Wright J, Small N. Potential social, economic and general health benefits of consanguineous marriage: the Born in Bradford Study. Eur J Publ Hlth 2013; doi: 10.1093/eurpub/ckt166

426 **Tables**

427

Ethnic background	Consan-guineous	Non-con sanguineous	All	Consanguinity (%)	Maternal age by ethnicity, mean ± SD, range
European	22 (3.3%)	31,042 (89.9%)	31,064 (88.3%)	0.07%	31.9 ± 5.2 15-50 years
Turkish	415 (61.5%)	1,994 (5.8%)	2,409 (6.9%)	17.2%	28.9 ± 5.6 15-47 years
Eastern Mediterra-nean / Maghreb	227 (33.6%)	817 (2.4%)	1,044 (3.0%)	21.8%	29.5 ± 6.4 16-44 years
African	0	112 (0.3%)	112 (0.3%)	0%	29.9 ± 5.2 18-41 years
Asian	11 (1.6%)	561 (1.6%)	572 (1.6%)	1.9%	31.6 ± 5.2 15-47 years
Maternal age mean ± SD, range	28.0 + 5.6* 16-44 years	31.7 ± 5.3 15-50 years			31.6 ± 5.4, 15-50 years

428

429

430 **Table 1:** Consanguinity, ethnicity and maternal age in mothers of 35,201 fetuses, 1993-2011.
431 Information was available on maternal age and ethnicity in all 675 fetuses with
432 consanguineous parents but was missing in 190 of the non-consanguineous group. Women in
433 consanguineous relationships were significantly younger than in non-consanguineous
434 relationships (*t-test, $p < 0.0001$).
435 (Information was available on the ethnic background of all 675 consanguineous fetuses and
436 on 99.5% of 34,716 fetuses with non-consanguineous parentage.)

437

438

439

Disorders diagnosed	Consan-guineous	%	Non-consan-guineous	%	All cases	%
Total cases	675	100%	34,716	100%	35,391	100%
Information on fetal outcome missing	107	15.9%	3,575	10.3%	3,682	10.4%
Information on fetal outcome available	568	84.1%	31,141	89.7%	31,710	89.6%
No disorder	504		30,248		30,755	
All congenital disorders	**62**	**10.9%**	**893**	**2.9%**	**955**	**3.0%**
Single gene defects	**37**	**6.51%**	**40**	**0.13%**	**77**	**0.24%**
Autosomal dominant	*0*		*15*	*0.05%*	*15*	*0.05%*
Autosomal recessive	*37*	*6.51%**	*22*	*0.07%*	*59*	*0.19%*
X-linked recessive	*0*		*3*	*0.01%*	*3*	*0.01%*
All chromosomal aberrations	**4**	**0.70%†**	**367**	**1.18%**	**371**	**1.17%**
Numerical chromosomal aberrations	*2*	*0.35%*	*322*	*1.03%*	*324*	*1.02%*
non-gonosomal	*1*	*0.18%*	*280*	*0.90%*	*281*	*0.89%*
gonosomal	*1*	*0.18%*	*42*	*0.13%*	*43*	*0.14%*
Structural chromosomal aberrations	*1*	*0.18%*	*23*	*0.07%*	*24*	*0.08%*
Mosaicism	*1*	*0.18%*	*22*	*0.07%*	*23*	*0.07%*
Molecular genetic disorders	**0**		**5**	**0.02%**	**5**	**0.02%**
Anatomically complex disorders with unclear genetic background	***21***	***3.70%***	***481***	***1.54%***	***502***	***1.58%***

440

441

442 **Table 2:** Frequencies and patterns of inheritance of major congenital disorders in
443 consanguineous and non-consanguineous pregnancies. Chi^2-tests, †p = 0.23, *p <0.0001

444

445

446

No	DOC	Diagnosis	M.o.i.	Fet aff. no	Mode/time of detection	Karyotype	US vis	Pregnancy outcome
First cousin cases with a probable causal relation to consanguinity … with a positive history								
1	1C	***Arthrogryposis***	AR/Rep	2	US 32 wks		+	NND 6 wks
2	1C	***Arthrogryposis***	AR/Rep	3	US 29 wks		+	NND 3 days
3	1C	Hydrops of unclear origin	Rep	2	US 13 wks		+	MTOP 19 wks
4	1C	Hydrops of unclear origin*	Rep	2	US 28 wks		+	IUD 30 wks
5	1C	Mitochondriopathy	AR/Rep	2	Diag den Postnatal		-	Delivery NND 11 months
6	1C	Glycogenosis II (Pompe) **	AR/Rep	2	US 21 wks		+	Delivery
7	1C	Meckel-Gruber syndrome	AR	2	US 22 wks		+	MTOP 22 wks
8	1C	Multicystic kidney disease	AR/Rep	2	US 21 wks		+	NND 1 day
9	1C	Multiple pterygium syndrome	Rep	2	FBA + US 31 wks	46,XX	+	IUD 33 wks
10	1C	Multicystic kidney disease	AR/Rep	2	US 23 wks		+	MTOP 23 wks
11	1C	ß-thalassaemia	AR/Rep	2	CVS 13 wks	46,XX	-	MTOP 17 wks
12	1C	Galactosaemia	AR/Rep	2	CVS 12 wks	46,XY	-	MTOP 15 wks
13	1C	Osteopetrosis	AR/Rep	2	CVS 12 wks	46,XY	-	MTOP 13 wks
14	1C	Fanconi anaemia	AR/Rep	2	CVS 13 wks	46,XY	-	MTOP 15 wks
15	1C	Micro-syndrome	AR/Rep	6	CVS 15 wks	46,XY	-	MTOP 16 wks
16	1C	Mucopolysaccharidosis VI	AR	2+fc..	AC 16 wks	46,XX	-	MTOP 22 wks
… without a positive history								
17	1C	Surfactant-b-deficiency	AR	1	Postnatal		-	NND 2 wks
18	1C	Citrullinaemia	AR	1	Postnatal		-	Delivery
19	1C	Meckel-Gruber syndrome	AR	1	US 12 wks		+	MTOP 13 wks
20	1C	Pierre-Robin-Syndrome	AR/Rep	1+f.c..	US 21 wks		+	Delivery
21	1C	Arthrogryposis-renal-cholestasis-syndrome	AR	1	Diagnosis postnatally	AC 26 wks: 46,XX		Delivery NND 3 months
Cases beyond first cousins ... with a positive history								
22	<1C	Glycogenosis type II (Pompe)	AR/Rep	2	Diag den		-	NND 7 months
23	<1C	***Glycogenosis type IV***	AR/Rep	2	Diag den		-	NND 14 wks
24	<1C	***SMA Werdnig-Hoffmann***	AR/Rep	2	CVS 12 wks	46,XY	-	MTOP 17 wks
25	<1C	***SMA Werdnig-Hoffmann***	AR/Rep	3	CVS 12 wks	46,XX	-	MTOP 14 wks
26	<1C	SMA Werdnig-Hoffmann	AR/Rep	3	CVS 20 wks	46,XX	-	MTOP 23 wks
27	<1C	***Adams-Oliver syndrome***	Rep	2	US 22 wks		+	MTOP 23 wks
28	<1C	***Adams-Oliver syndrome***	Rep	3	US 13 wks		+	MTOP 14 wks
29	<1C	Unclear syndrome with severe mental retardation	AR/Rep	2	Postnatal		-	Delivery
30	<1C	Cockayne syndrome	AR/Rep	2	CVS 11 wks	46,XX		MTOP 19 wks
31	<1C	Microcephaly	Rep	2	US 37 wks		+	MTOP 37 wks
32	<1C	COFS	AR/Rep	2	US 31 wks			MTOP 31 wks
33	<1C	Unclear syndrome with cleft palate and skeletal dysplasia	AR/Rep	2	US 16 wks		+	MTOP 16 wks
34	<1C	Unclear skeletal dysplasia (OI?)	AR/Rep	2	US 26 wks		+	Delivery
… without a positive history (no preceding affected fetus/child)								
35	<1C	***Glycogenosis type IV***	AR/Rep	1	Postnatal		-	NND 10 wks
36	<1C	Meckel-Gruber syndrome	AR	1	US 12 wks		+	MTOP 14 wks
37	<1C	Microcephaly	Rep	1+ fam.c.	US 21 wks		+	Delivery

447

Table 3: Overview of 37 cases (group A) showing a probable causal association of the diagnosed anomaly with consanguinity.

Cases 4 and 6 were dizygotic twin pregnancies: *in case 4 one of the twins had intrauterine demise at 34 weeks; **in case 6 first signs were seen at 21 weeks with diagnosis made postnatally; in both cases the co-twins were normal. In the 8 cases of the 4 women printed in bold (cases 1 and 2, cases 24 and 25, cases 27 and 28 and cases 35 and 23), the couples had several children with an identical diagnosis in different pregnancies. Three of these 4 women had a third affected fetus not listed here as Table 3 is based only on cases we examined in our centre. Column 5 gives the number the previous affected fetuses of the couple investigated. In 9 of the 37 cases the anomaly occurred in the family for the first time.

DOC, degree of consanguinity; 1C, first cousin; <1C, beyond first cousin; mgt molecular genetic test; Fet aff. No, fetus affected number; SMA, spinal muscular atrophy: COFS, cerebro-oculo-facial syndrome, AR autosomal recessive; Rep, repetitive case; fam.c., familial case; CVS, chorionic villous sampling; AC, amniocentesis, US, ultrasound; wks, weeks; Diag den, diagnostics declined (pregnant woman did not accept invasive procedure); MTOP, medical termination of pregnancy; IUD, intrauterine death; NND, neonatal death.

No.	DOC	Diagnosis	Fet aff no	Mode/time of detection	Karyotype	US vis	Pregnancy outcome
First cousin cases with a possible causal relation to consanguinity … without a positive history							
38	1C	Hydrops of unclear origin	1	US 23 wks CVS+FBA	46,XX	+	IUD 30 wks
39	1C	Hydrops of unclear origin	1	US 11 wks CVS	46,XX	+	MTOP 14 wks
40	1C	Hydrops of unclear origin	1	US 19 wks		+	MTOP 22 wks
41	1C	Hydrops of unclear origin	1	US 20 wks		+	IUD 28 wks
42	1C	Hydrops of unclear origin	1	US 23 wks		+	IUD 23 wks
43	1C	Hydrops of unclear origin	1	US 16 wks		+	IUD 16 wks
44	1C	Hydrops, CHD	1	US 19 wks		+	MTOP 20 wks
45	1C	Heterotaxy syndrome	1	US 22 wks		+	MTOP 22 wks
46	1C	CHD: Taussig-Bing	1	US 22 wks		+	MTOP 23 wks
47	1C	Complex syndrome: Heart, CNS. Prior pregnancy hydrocephalus	1+1 diffe-rent	US 20 wks AC	46,XX	+	MTOP 23 wks
48	1C	Cleft lip and palate	1	US 21 wks AC	46,XY	+	Delivery
Cases beyond first cousin with a possible causal relation to consanguinity … without a positive history							
49	<1C	Unclear syndrome with hydrothorax	1	US 14 wks CVS	46,XY	+	Delivery
50	<1C	Unclear syndrome, CHD, SUA, stigmata	1	US 22 wks		+	MTOP 22 wks
51	<1C	Complex anomaly of CNS	1	US 24 wks		+	Delivery
52	<1C	AV septal defect + CDH	1	US 22 wks		+	Delivery
53	<1C	Complex urogenital anomaly	1	US 21 wks		+	Delivery
54	<1C	Heterotaxy syndrome	1	US 22 wks		+	Delivery
55	<1C	CDH, history of 5 abortions	1	US 22 wks		+	NND day 1
56	<1C	Hydrocephalus; prior pregnancy: unclear syndrome, death 1 year	1+1 diffe-rent	US 16 wks AC	46,XX	+	MTOP 17 wks
First cousin cases with an improbable causal relation to consanguinity … without a positive history							
57	1C	Klinefelter syndrome no clinical symptoms	1	US 17 wks AC	47,XXY	-	Delivery
58	1C	Paternal balanced translocation	1	US 13 wks CVS	5 p- (cri du chat)	-	MTOP 14 wks
59	1C	Bilateral renal agenesis	1	US 21 wks		+	MTOP 22 wks
60	1C	Down syndrome enlarged NT	1	US 13 wks CVS	47,XY +21	+	MTOP 18 wks
61	1C	Adactyly dig. 2-4 right hand	1	US 21 wks		+	Delivery
62	1C	Ebstein's anomaly chromosomal anomaly	1	US 21wks AC+FBA	mosaicism 46,XY/ 47,XY,+6	+	Delivery

Table 4: Overview of 19 cases with major anomalies (nos. 38-56, group B) showing a possible causal association with consanguinity as well as 6 cases with major anomalies (nos. 57-62, group C) showing an improbable association with consanguinity. Column 4 gives the number the previous affected fetuses of the couple investigated

DOC, degree of consanguinity; Fet aff no , fetus affected number; US vis, visibility by ultrasound; wks, weeks; CVS, chorionic villous sampling; US, ultrasound; IUD, intrauterine death; MTOP, termination of pregnancy for medical reasons; 1C, first cousin; <1C, beyond first cousin; AV septal defect, atrio-ventricular septal defect; CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; CNS, central nervous system; SUA, single umbilical artery; CVS, chorionic villous sampling; AC, amniocentesis; US, ultrasound; wks, weeks; MTOP, medical termination of pregnancy; IUD, intrauterine death; NND, neonatal death; NT, nuchal translucency.

		Consang.	Non-consang.	All cases
Prenatal	No. of congenital defects	62	893	955
	IUD	6 (9.7%)	44 (4.9%)†	50 (5.2%)
	MTOP	31 (50.0%)	544 (60.9%)	575 (60.2%)
	Survival to term	25 (40.3%)	305 (34.2%)	330 (34.6%)
Postnatal	NND within week 1	3 (4.8%)	20 (2.2%)	23 (2.4%)
	Postneonatal survival more than one week	22* (35.5%)	285 (31.9%)	307 (32.2%)

Table 5: Pregnancy outcomes of fetuses with major anomalies conceived by consanguineous and non-consanguineous parents.

*Another six babies (nos.1, 5 ,17 ,22 ,23 ,35) died after the first week but within the first year of life because of consanguinity-associated diseases.

†Chi^2-test, p = 0.12