Author's response to reviews

Title: Consanguinity and Reproductive Health among Arabs

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Author's response to reviews: see over
Reproductive Health Editorial Team,

Dear Dr Kulier,

Thank you for your email message on 7th July that included the reviewers’ comments to the manuscript number 1293911697272776 - Consanguinity and Reproductive Health among Arabs. The authors would like to thank the reviewers for their valuable comments. The following is a detailed, point to point description of the amendments done in the manuscript according to the reviewers’ comments.

Response to Professor Bittles comments:

Response to first comment: The following sentences have been added:
Page 2, at the end of introduction: ‘The custom of endogamy among individuals belonging to the same tribe (hamula or kabeela) is and has been strongly favoured among Arabs, with the consequence of unequal distribution of founder mutations among the population. A large number of studies into the effects of consanguinity on health and disease have not taken such discrepancies into consideration’

Page 5, 2nd paragraph on consanguinity and autosomal recessive disease with inclusion of new reference number 77: In many parts of the Arab world the society is still tribal. This has made the epidemiology of genetic disorders complicated, as many families and tribal groups are descended from a limited number of ancestors and some conditions are confined to specific villages, families, and tribal groups, leading to an unusual burden of genetic diseases in these communities [77].

Response to Specific comments and queries to authors:

1- We definitely agree with professor Bittles, but due to the dearth of studies in this Region, we had to include many of those that did not properly categorise consanguineous marriages, but we indicated precisely the terminology used for each study mentioned in this review. We have added the following paragraph in response to this comment in the first paragraph on page 4:
Research on the association of consanguinity with the different parameters of reproductive health in Arab countries is limited, both in quantity and in quality. Many studies fail to indicate clearly the different categories of consanguineous marriages in their methodology and thus the results are presented for consanguineous marriages as a single entity with the conclusions relying on a simple consanguineous versus non-consanguineous dichotomy. Given the wide range of F values in the ‘consanguineous’ group (F = 0.0156-0.125), with second cousin offspring (F = 0.0156) closer to non-consanguineous (F = 0) than to first cousins (F = 0.0625) or double first cousins (F = 0.125), such comparisons between consanguineous and non-consanguineous are thus not accurate. However, owing to the dearth of publications in the field among Arabs, this review will mention these studies with clear indication of the categories of consanguinity that are being compared.

2- We agree with Professor Bittles that a consanguinity percentage of 36.6% for the 451 disorders in the CTGA database for the mentioned countries is too low when compared to the higher consanguinity rates in the same countries.
mentioned in table 1, since 63% of all these disorders are autosomal recessive. The expected consanguinity rate among autosomal recessive cases would be around 85%, and 25-30% among other genetic conditions such as X-linked recessive, chromosomal and autosomal dominant (Reference 76: Hamamy et al. Consanguinity and genetic disorders. Profile from Jordan. Saudi Med J. 2007; 28:1015-7). The reason for this low percentage is that not all the studies that feed the CTGA database cite the consanguinity status among the families of affected. The authors have therefore decided to omit the sentence referring to this low percentage since it does not reflect the true situation of the association of consanguinity with genetic disorders. On the other hand, the proportion of recessive disorders of 63% in the CTGA database confirms the fact that different autosomal recessive disorders are of major preponderance among all genetic diseases among Arabs. The paragraph pointing to this percentage is thus retained.

3- We agree with professor Bittles, the references from South America and France have been deleted.

4- The following has been added as requested by the comment on page 5, paragraph 2: ‘This finding is unsurprising, given the limited control for concomitant variables such as socioeconomic status, maternal education, birth intervals and public health facilities and practices in most consanguinity studies.

5- The sentence was amended to ‘there may be equality.’ On page 5, paragraph 2.

6- The following was inserted as requested by the reviewer on page 5, paragraph 3: ‘particularly for rare autosomal recessive disease genes, because for common recessive conditions, there is a high chance that the abnormal gene may be carried by unrelated spouses and may be expressed in their progeny.’

Minor Comments to authors

1- Spelling corrected and the references corrected
2- The reference was changed as requested
3- The terms were amended
4- The following was inserted as requested on page 4, paragraph 2: estimated birth defects to be >69.9/1000 livebirths in most Arab countries, as opposed to <52.1/1000 livebirths in Europe, North America and Australia

5- The sentence was changed on page 6, paragraph before the last to: ‘Similarly, in various ethnic groups from Mauritania (including: Soninkes, Poulard, Maures, Wolofs, and black Maures) consanguineous couples had averages of fertility significantly higher than those of non consanguineous couples.’
Response to Professor Inhorn comments:

**Major Compulsory Revisions:**

**First point on the CTGA database:**
The abrupt mention of CTGA in the abstract might have caused some misconception over the exact nature of the CTGA Database. Corrections were made in various positions in the manuscript to alleviate the confusion that CTGA is a database archiving studies on consanguinity in the Arab World. The Database is an extensive collection of literature on the occurrence of 100s of genetic disorders in Arab people irrespective of the status of consanguinity. The Database has been discussed in detail in various publications including [Tadmouri et al. Nucleic Acids Res. 2006; 34(Database issue):D602-6.] and references 79,80,81 in the submitted manuscript. In order to alleviate the misconception about the CTGA data base the following paragraphs have been inserted:

1- At the end of the abstract: ‘Worldwide, known dominant disorders are more numerous than known recessive disorders. However, data on genetic disorders in Arab populations as extracted from the Catalogue of Transmission Genetics in Arabs (CTGA) database indicate a relative abundance of recessive disorders in the region that is clearly associated with the practice of consanguinity’.

2- Page 6, 2nd paragraph: ‘An analysis of data in the Catalogue for Transmission Genetics in Arabs (CTGA), a database on genetic disorders in Arab populations maintained by the Centre for Arab Genomic Studies, indicates that in contrast to international databases, the overwhelming proportion….

3- In the conclusive remarks: ‘The CTGA Database on genetic disorders in Arab populations offers a clear…

**Second point:** "The article does not add much to the existing literature". The article is the most extensive compilation of studies on consanguinity in Arab people, many of which are unreachable to the average reader. The article also paves the way for future analyses on consanguinity in countries for which data are either unavailable or haven't been produced using standard procedures. 

"Although autosomal recessive… these kinds of defects are not described in any detail." At the end of page 5 examples of some autosomal recessive disorders are added quoted from the references suggested by the reviewer: “.There are disorders that are specifically prevalent among the Arabs either uniformly or in certain locations such as Bardet-Biedl syndrome, Meckel-Gruber syndrome, spinal muscular atrophy, osteopetrosis and renal tubular acidosis, Sanjad-Sakati syndrome, and congenital chloride diarrhea”

"consanguinity and male infertility outcomes is not included in the article”: the reference on male infertility was added in the 2nd paragraph on page 7.

**Third point:** The table can be enhanced by graying columns with important content such as Country/1C/Overall; this has to be done in agreement with the technical publishing conditions of the journal. In addition, the document can be provided separately in PDF format to overcome any incompatibilities among word processing programs faced by the reviewer.
Fourth Point: This has been answered in points 1 and 2.

Minor Essential Revisions:
Prof. Inhorn seems to be very concerned with the paragraph before the last under "Consaguinity in Arab Populations". She used the statement "backward, inbreeding tribal peoples" because of our sentence at the beginning of the paragraph saying "...favoring consanguineous marriages among the new generations just as strongly as they did among the older generations...". To alleviate this misconception, we have added the following notes on the rationales for cousin marriages among Arabs and the relevant literature in page 3, paragraph before last: ‘Consanguineous marriages among Arabs are respected because it is thought that they promote family stability, simplify financial premarital negotiations, offer a greater compatibility between the spouses and other family members, offer a lesser risk of hidden financial and health issues, and maintain the family land possessions[3,24,25]. Among 390 women attending reproductive health clinics in Jordan, consanguinity was protective against violence during pregnancy [26].’

Other amendments:
A recent publication on consanguinity rate in Syria is added to the table.

The format of some of the generic references uploaded on Reference Manager keeps changing whenever the references are amended, these could be corrected in the final steps.
We are herewith resubmitting the manuscript including all amendments requested by the reviewers to be considered for publication in ‘Reproductive Health’.

Best regards

Hanan Hamamy
Ghazi Tadmouri