Diagnostic and perinatal outcomes in consanguineous couples with a structural fetal anomaly

Mone, Fionnuala; Doyle, Samantha; Ahmad, Asfa; Subieh, Hala Abu; Hamilton, Susan; Allen, Stephanie; Marton, Tamas; Williams, Denise; Kilby, Mark

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TITLE: Diagnostic and perinatal outcomes in consanguineous couples with a structural fetal anomaly – a cohort study

AUTHORS: Fionnuala MONE PhD,[a] Samantha DOYLE MD,[b] Asfa AHMAD MSc,[b] Hala ABU SUBIEH MD,[a] Susan HAMILTON PhD,[b] Stephanie ALLEN PhD,[b] Tamas MARTON MRCPath,[c] Denise WILLIAMS,[b] Mark D KILBY MD[a,d]

AFFILIATIONS:

a. Fetal Medicine Centre, Birmingham Women's and Children's NHS Foundation Trust, Edgbaston, Birmingham B15 2TG, UK
b. West Midlands Regional Genetics Laboratory and Clinical Genetics Service, Birmingham Women's and Children's NHS Foundation Trust, Edgbaston, Birmingham B15 2TG, UK
c. West Midland's Perinatal Pathology Service, Birmingham Women's and Children's NHS Foundation Trust, Edgbaston, Birmingham B15 2TG, UK
d. Institute of Metabolism and Systems Research, College of Medical & Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

CORRESPONDING AUTHOR: Dr Fionnuala Mone. Fetal Medicine Centre, Birmingham Women's and Children's NHS Foundation Trust, Edgbaston, Birmingham B15 2TG, UK E: fionnuala.mone@nhs.net T: +44-121-472-1377

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ABSTRACT

INTRODUCTION: Consanguineous unions occur when a couple are related outside marriage. It is a common practice amongst UK Pakistanis and is associated with adverse genetic and perinatal outcomes for affected offspring. The objectives of this study were to evaluate the; (i) background characteristics; (ii) uptake of prenatal and postnatal investigation and; (iii) diagnostic outcomes of UK consanguineous couples presenting with a fetal structural anomaly (FSA).

MATERIALS AND METHODS: This was a retrospective and partly prospective cohort study comparing consanguineous (n=62) and non-consanguineous (n=218) pregnancies with current or previous FSAs reviewed in a UK prenatal genetic clinic from 2008-2019. Outcomes were compared using odds ratios (OR).

RESULTS: Most consanguineous couples were of Pakistani ethnicity OR 29 (95% CI, 13-62) and required use of an interpreter OR 9 (95% CI, 4-20). In the consanguineous group, the uptake of prenatal invasive testing was lower; OR 0.4 (95% CI, 0.2-0.7) and the number declining follow-up OR 10 (95% CI, 3-34) was greater, compared to the non-consanguineous group. This likely explained the lower proportion of consanguineous couples where a final definitive unifying diagnosis to explain the FSAs was reached OR 0.3 (95% CI, 0.2-0.6). When a diagnosis was obtained in this group, it was always postnatal and most often using genomic sequencing technologies OR 6 (95% CI, 1-27). The risk of perinatal death was greater OR 3 (95% CI, 1-6) in the consanguineous group, as was the risk of FSA recurrence in a subsequent pregnancy OR 4 (95% CI, 1-13). There was no difference in the uptake of perinatal autopsy or termination of pregnancy between groups.

CONCLUSIONS: Consanguineous couples are a vulnerable group in the prenatal setting. Although adverse perinatal outcomes in this group are more common secondary to congenital anomalies, despite the evolution of genomic sequencing technologies, due to a lower uptake of prenatal testing it is less likely that a unifying diagnosis is obtained and recurrence can occur. There is a need for proactive genetic counselling and education from the multi-disciplinary team, addressing language barriers as well as religious and cultural beliefs in an attempt to optimise reproductive options.

KEYWORDS: CONSANGUINEOUS; CONGENITAL ANOMALY; AUTOSOMAL RECESSIVE; PAKISTANI; TERMINATION OF PREGNANCY; AUTOPSY; GENOMIC TESTING; FETUS

KEY MESSAGE: UK consanguineous unions have a lower uptake of prenatal investigation and hence establishment of a prenatal diagnosis, with diagnoses obtained postnatally and predominantly via genomic sequencing. There was no difference in uptake of termination or autopsy compared to non-consanguineous groups.

INTRODUCTION

Since the latter half of the 20th century, the United Kingdom (UK) has developed into an ethnically diverse population.[1] Census data suggest that the second largest ethnic group in the West Midlands is of Pakistani origin.[2,3] Consanguineous unions occur when a couple are related outside of marriage as second cousins or greater.[4] The majority of Pakistanis in Birmingham are from the North-Eastern Kashmir region of Pakistan/India where consanguinity occurs in over 60% of unions and is mainly of first-cousin nature within pre-defined traditional groupings known as *Biraderi*.[5-7] The reasons for favouring such unions are based upon traditional cultural, religious, political, socio-economical and geographical motivations.[1,7] Over 90% of British Pakistanis identify as Muslim with the majority of UK Muslims of Pakistani or Bangladeshi heritage.[8] Consanguineous marriages are also common in other UK ethnic minorities such as Irish Travellers, Middle Eastern, Iranian and North African Groups.[1,4] Consanguinity lends itself to an increased risk of genomic homozygosity, with a higher incidence of rare autosomal recessive disorders, with 30% of such disorders occurring in Pakistani children in the UK.[6,9] This poses a major public health concern with high rates of infant death and disability secondary to congenital anomaly which is the commonest cause of childhood mortality in this group.[10,11] There is currently no UK consensus regarding the provision of genetic counselling services for consanguineous couples relating to reproductive risk.[12] It is important for fetal medicine specialists, prenatal geneticists, midwives and genetic counsellors to have an awareness of the religious and cultural preferences of couples in consanguineous unions so that optimal and tailored management can be provided.[4] There is a paucity of evidence exploring the management and outcomes within this setting, hence the objectives of this study were to evaluate the; (i) background characteristics; (ii) uptake of investigation and; (iii) diagnostic outcomes of consanguineous couples presenting with fetuses with structural anomalies.

MATERIALS AND METHODS

This retrospective and part prospective (2018 onward) cohort study included couples referred to a combined fetal medicine genetics clinic with either a history of or a current fetal structural anomaly in the Birmingham Women's and Children's NHS Foundation Trust, UK between August 2008 and December 2019. This tertiary prenatal centre serves a population of over five million within the West Midlands region and triages referrals from 17 obstetric centres. The indications for referral, clinical pathway [Figure 1] and overall outcomes of this clinic have been described previously.[13] Typically women attending the clinic will have undergone assessment and prenatal invasive testing and chromosome microarray (CMA) by the referring fetal medicine specialist but if invasive testing is then re-offered and if declined in the specialist clinic, a plan is made to initiate CMA from cord blood taken at delivery or fetal/placental DNA extraction with parental DNA banking, moving on to trio exome sequencing or targeted testing dependent upon the multidisciplinary team (fetal medicine subspecialist, clinical geneticist, genomic scientist, genetic counsellor and pathologist) consensus. A proportion of the cohort typically referred to this service may be captured at their local institution with genetic work-up/testing occurring at that point, hence the cohort we present in this study only reflects those cases which were referred to the specialist joint-clinic. The West Midlands Regional Genetics Service is unique in that it is one of the few services which employs two genetic counsellors who's remit is to work primarily with families that practice customary consanguineous marriage within geographic areas of the West Midlands where the Pakistani community lives predominantly. These counsellors have firm traditional links with the West Midlands Fetal Medicine Centre, can speak the appropriate languages and have an understanding of the community and family structures.

The study cohort was divided into those that were consanguineous and non-consanguineous (based on family pedigree). Demographics were obtained from computerized systems for fetal ultrasound (Viewpoint 6, GE, 2019) and clinical genetics notes and were recorded in an anonymized database. Data collection for each case was continued until completion of the study. Ethnicity was self-reported and classified according to the classification of the UK Office of National Statistics (UK ONS). Genetic laboratory diagnoses were made based upon clinical guidelines for prenatal diagnostic testing and variants from sequencing (single gene/panel testing or exome sequencing) were classified in line with the American College of Medical Genetics.[14-16]

Statistical Analysis

Intergroup comparisons for continuous variables with a parametric distribution were made using t-test to determine significant differences between the data sets. For such data, mean values and standard deviations are described. Categorical data were analysed using Fisher's exact test and odds ratios and 95% confidence intervals. Significance was taken as $p < 0.05$ unless otherwise stated.

Ethical Approval

Due to the anonymised and descriptive nature of the study, it was deemed suitable for registration as an audit without the requirement for ethical approval by the Birmingham Women's and Children's NHS Foundation Trust Clinical Audit Registration and Management System (Audit Code: CARMS-30672).

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RESULTS

In total n=280 pregnancies were included in the cohort (n=62 (22.1%) consanguineous and n=218 (77.9%) non-consanguineous). Demographics of both groups are demonstrated in Table 1. In the consanguineous group, most couples were of Pakistani n=40/62 (64.5%) or Bangladeshi n=10/62 (16.1%) ethnicity; OR 23 (95% CI, 11-47), were multiparous, required use of an interpreter and had personally experienced a previous perinatal death; OR 4 (95% CI, 2-4). They were more likely to be referred to the clinic with recurrence of a structural anomaly; OR 4 (95% CI, 2-8).

The uptake of investigations is demonstrated in Table 2. Couples in the consanguineous group were less likely to undergo an invasive prenatal test and more likely to decline follow-up in the pregnancy or postnatal period. There was a trend towards a lower uptake of perinatal autopsy but this was not significant n=14/35 (40%) consanguineous vs. n=50/98 (51%) non-consanguineous although this was not significant (p=0.35).

Pregnancy outcomes are demonstrated in Table 3 and show that in consanguineous couples it was less likely that a unifying diagnosis would be obtained and where it was, in all instances this was postnatally (following clinical examination/autopsy and/or DNA extraction from cord-blood at delivery or fetal/placental tissue). Of the n=14 diagnoses made, two were clinical based upon a previous phenotypic anomaly (i.e. Fryns Syndrome and Asphyxiating Thoracic Dystrophy) with the remaining cases of chromosomal (n=2) or single gene origin (n=10) diagnosed on genomic sequencing (targeted testing n=2 or exome sequencing n=10), of which n=11/12 (91.7%) were inherited in an autosomal recessive (biallelic) fashion with the majority representing syndromes of a life-limiting nature n=8/12 (66.7%) [supplementary Table 1]. Consanguineous couples were more likely to experience a perinatal death in the index pregnancy with uptake of termination of pregnancy (TOP) no different between groups, including that of late TOP 14.5% (n=9/62) vs. 16.9% (n=37/218) OR 0.8 (95% CI, 0.4-2) p=0.65. Consanguineous couples were more likely to present again in a subsequent pregnancy with the same structural fetal anomaly 4 (95% CI, 1-13).

DISCUSSION

This cohort study of structural fetal anomalies in consanguineous unions in a UK prenatal genetic clinic setting reveals that, in our centre, most couples were of Pakistani ethnicity, more likely to experience perinatal loss and require the use of an interpreter. While the uptake of prenatal invasive testing was lower, there was no difference in the uptake of fetal autopsy or TOP. Amongst consanguineous couples, it was less likely that a unifying diagnosis would be reached, with any diagnoses made postnatally and the majority being single gene disorders of a lethal autosomal recessive nature. Those in the consanguineous group were more likely to present with recurrence of an anomaly.

Such a high incidence of perinatal death has been previously reported in the literature.[10-12, 17] Although there was a trend toward a lower uptake of autopsy in the consanguineous group, there was no difference between groups. The majority of UK Pakistanis and Bangladeshis identify as Muslim.[8] An Islamic *fatwa* (ruling) in 1982 supported autopsy in instances where benefit outweighed drawbacks.[18] Despite this, there are traditional cultural Muslim beliefs which have led to a typically low uptake of perinatal autopsy.[18] Similarly, in our study, there was no difference in rates of TOP, a practice which in Sunni Islamic law is permitted when there is a maternal risk or lethal anomalies in the fetus prior to the 120th day of gestation, regarded as the period of ensoulment.[19] Evidence suggests that in certain instances, UK Pakistani couples may be becoming more open to TOP, possibly because they are increasingly second or third generation and have a greater understanding of the implications of consanguinity than their relatives.[20,21]

Despite no differences between groups with regards TOP and autopsy uptake, the uptake of prenatal invasive testing was significantly lower in the consanguineous group and more couples declined any further testing or appointments, leading to any unifying diagnoses being obtained in the postnatal period and a lower proportion of diagnoses being reached overall. This may be due to the challenge of providing detailed genetic counselling via an interpreter as well as a tendency for those of Pakistani and Bangladeshi ethnicity to be in a lower socioeconomic group.[7,19,22] This added to layers of parental anxiety around complying with religious and cultural Islamic beliefs may lead to a more limited understanding of the role of prenatal genetic testing.[7,19,22] In instances where couples are struggling with decisions surrounding autopsy and TOP, liaison with the Muslim chaplain may be beneficial.[23]

Moving forward, options of minimally invasive autopsy[23] and non-invasive prenatal diagnosis, particularly when performed prior to the period of ensoulment to permit timely TOP are investigations which Muslim communities appear to be open to.[24] In the era of prenatal Next Generation Sequencing more single gene disorders may be prospectively identified,[25,26] permitting knowledge of carrier status with testing strategies extending to those only requiring parental samples for lethal autosomal recessive conditions.[27] There is emerging evidence to suggest that attitudes amongst UK Pakistanis to within-*Biraderi* marriages are changing, with a proportion seeking knowledge of carrier status possibly to potentially facilitate partner selection.[6] The use of genetic mutation databases for common pathogenic variants and syndromes identified in consanguineous populations such as the Irish Travellers and Ashkenazi Jews can aid in targeted carrier screening and obtaining a prompt molecular diagnoses. Such a database is also in existence for the Pakistani community and may aid multi-disciplinary teams in mitigating the impact of consanguineous unions on perinatal morbidity and mortality.[28-30]

Proactive genetic counselling pre and post-test and regarding reproductive choices is required for consanguineous couples anticipated to have or who have had a fetus with an autosomal recessive disorder. This includes addressing language barriers and understanding cultural and religious beliefs around decision making to limit the distress and impact for couples and empower them to make informed decisions. While, the increased need for an interpreter in the consanguineous group was likely secondary to ethnicity, clinicians must be aware of the increased need for provision of this service to facilitate effective counselling. Addressing the aforementioned barriers is the responsibility of the multi-disciplinary team so that the potential implications for the child are clearly discussed as well as future options to reduce recurrence risk inclusive of non-invasive prenatal diagnosis (in compound heterozygotes) and pre-implantation genetic diagnosis.[31] Such strategies may limit the high levels of recurrence seen in our study. Consideration may also be given to genetic counselling being provided by those of the same ethic background who speak the same language, as this has previously been shown to improve the uptake of genetic services.[32] Challenges with regards such proactive counselling are that in the absence of a family history it may not reach at-risk couples. To aid this, education of community-based healthcare workers is needed to flag such couples to the genetics service, with a view to obtaining a detailed family history, including determining which regions couples originate from so that targeted cascade testing, specific to such regions

could be offered.[12,33,34] Such a strategy which has been successful in the recognition and reduction of beta-thalassemia.[34,35]

The strength of this study is that it is one of limited studies addressing the uptake of investigation and outcomes in consanguineous unions. The clinic where the study was performed is based in a leading international fetal medicine and genetic centre offering advanced genomic strategies which is well versed in the management of consanguineous couples due to a high incidence in this region.[36,37] Throughout the study the same clinicians (M.D.K. & D.W.) and scientists (S.H. & S.A.) were involved in the running of the clinic and data was followed up over a decade to ensure that all information was complete. Weaknesses include the study's predominantly retrospective nature as well as the potential for selection bias as not all consanguineous couples with anomalous fetuses would have been referred in, with referral at the discretion of the referring clinician. Also, as the study took place over a decade, the impact of prenatal genomic sequencing in the consanguineous group cannot be fully appreciated. There were still a relatively high number of couples of Pakistani and Bangladeshi origin in the non-consanguineous group, reflecting that a proportion do not practice consanguineous marriage or there may have been couples which did not disclose or were not aware of consanguinity. Also, not all consanguineous couples in the cohort may have identified as Muslim, hence potential religious foundations for statistical differences between group can only be speculative. One technique to test for consanguinity is to perform single nucleotide polymorphism analysis to reveal areas of homozygosity, however prospective consent had not been provided for this in this instance.[38]

CONCLUSION

This study supports UK public health concerns surrounding the consequences of consanguineous unions, secondary to a high incidence of perinatal lethal autosomal recessive disorders. Reduced uptake of prenatal testing in this group limits the opportunity to obtain a unifying diagnosis. To optimise reproductive options, the multi-disciplinary team must be proactive in providing informative counselling incorporating religious and cultural beliefs and addressing barriers of language and education to optimising early diagnosis via the use of modern genomic technologies.

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REFERENCES

1. Corry PC. Consanguinity and prevalence patterns of inherited disease in the UK Pakistani community. *Hum Hered.* 2014;77(1-4):207-16.
2. Birmingham City Council Population and Census. KS201 ethnic group. 2011. https://www.birmingham.gov.uk/downloads/file/9741/2018_ks201_ethnic_group. Accessed 27th April 2020.
3. Department for Communities and Local Government. The way forward: an independent review of the governance and organisational capabilities of Birmingham City Council: Supporting analysis. December 2014. Accessed from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/390167/Birmingham_Evidence_Pack__for_publication__FINAL.pdf on 29th April 2020
4. Mone F, McAuliffe FM, Lynch SA. A perinatal approach to genetic disorders in Irish Travellers: A review. *Eur J Obstet Gynecol Reprod Biol.* 2018;228:43-47.
5. Jabeen N, Malik S. Consanguinity and Its Sociodemographic Differentials in Bhimber District, Azad Jammu and Kashmir, Pakistan. *J Health Popul Nutr.* 2014; 32(2): 301–313.
6. Small N, Bittles AH, Petherick ES, Wright J. Endogamy, consanguinity and the health implications of changing marital choices in the UK Pakistani community. *J Biosoc Sci.* 2017;49(4):435-446.
7. Bhopal RS, Petherick ES, Wright J, Small N. Potential social, economic and general health benefits of consanguineous marriage: results from the Born in Bradford cohort study. *Eur J Public Health.* 2014;24(5):862-9.
8. The Muslim Council of Britain. British Muslims in Numbers. 2015. Accessed from: https://www.mcb.org.uk/wp-content/uploads/2015/02/MCBCensusReport_2015.pdf on 18th September 2020
9. Hutchesson AC, Bundey S, *et al*. A comparison of disease and gene frequencies of inborn errors of metabolism among different ethnic groups in the West Midlands, UK. *J Med Genet.* 1998;35(5):366-70.
10. 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 Oct 19;382(9901):1350-9.

11. Bundey S, Alam H, Kaur A, *et al*. Why do UK-born Pakistani babies have high perinatal and neonatal mortality rates? *J Community Genet.* 2016;7(1):65-79.
12. Darr A, Small N, Ahmad WI, *et al*. Addressing key issues in the consanguinity-related risk of autosomal recessive disorders in consanguineous communities: lessons from a qualitative study of British Pakistanis. *J Community Genet.* 2016;7(1):65-79.
13. Mone F, O'Connor C, Hamilton S, *et al*. Evolution of a prenatal genetic clinic-A 10-year cohort study. *Prenat Diagn.* 2020;40(5):618-625.
14. Association for Clinical Genomic Science. Prenatal Diagnosis Best Practice Guidelines (2009) v1.00/ Available from: https://www.acgs.uk.com/quality/best-practice-guidelines/ Accessed on 20th February 2020
15. Association for Clinical Genomic Science. Professional guidelines for clinical cytogenetics and clinical molecular genetics QF-PCR for the diagnosis of aneuploidy best practice guidelines (2012) v3.01 (26) (PDF) ACC/CMGS best practice guidelines for QF-PCR-based diagnosis of aneuploidy. Accessed from: https://www.acgs.uk.com/quality/best-practice-guidelines/ on 9th April 2020
16. Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405-24.
17. Kapurubandara S, Melov S, Shalou E, Alahakoon I. Consanguinity and associated perinatal outcomes, including stillbirth. Aust N Z J Obstet Gynaecol 2016; 56(6): 599–604
18. Al Adnani M. Can we improve the rate of autopsies among Muslims? *BMJ* 2006; 332(7536):310
19. Al-Matary A, Ali J. Controversies and considerations regarding the termination of pregnancy for foetal anomalies in Islam. *BMC Med Ethics.* 2014;15:10.
20. Ahmed S, Ahmed M, Sharif SM, *et al*. Attitudes towards prenatal testing and termination of pregnancy in British Pakistani parents and relatives of children with recessive conditions in the UK. *Prenat Diagn.* 2012; 32: 1-6
21. Ahmed S, Hewison J, Green JM, *et al*. Decisions about testing and termination of pregnancy for different fetal conditions: a qualitative study of European White and Pakistani mothers of affected children. *J Genet Couns.* 2008;17(6):560-72.

22. Gov.UK. Ethnic Groups by Socioeconomic Status. Accessed from: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/socioeconomic-status/latest#ethnic-groups-by-socio-economic-status on 30th April 2020.
23. Lewis C, Latif Z, Hill M, *et al*. We might get a lot more families who will agree": Muslim and Jewish perspectives on less invasive perinatal and paediatric autopsy. *PLoS One.* 2018;13(8):e0202023.
24. Ahmed S, Jafri H, Rashid Y, *et al*. Attitudes towards non-invasive prenatal diagnosis among obstetricians in Pakistan, a developing, Islamic country. *Prenat Diagn.* 2017;37(3):289-295.
25. Monies D, Abouelhoda M, Assoum M, *et al*. Lessons Learned from Large-Scale, First-Tier Clinical Exome Sequencing in a Highly Consanguineous Population. A*m J Hum Genet.* 2019;104(6):1182-1201.
26. Charng WL, Karaca E, Coban Akdemir Z, *et al*. Exome sequencing in mostly consanguineous Arab families with neurologic disease provides a high potential molecular diagnosis rate. *BMC Med Genomics*. 2016;9(1):42.
27. Stals KL, Wakeling M, Baptista J, *et al*. Diagnosis of lethal or prenatal-onset autosomal recessive disorders by parental exome sequencing. *Prenat Diagn.* 2018;38(1):33-43.
28. Qasim I, Ahmad B, Khan MA, *et al*. Pakistan Genetic Mutation Database (PGMD); A centralized Pakistani mutome data source. *Eur J Med Genet.* 2018;61(4):204-208.
29. Zlotogora J, Patrinos GP, Meiner V. Ashkenazi Jewish genomic variants: integrating data from the Israeli National Genetic Database and gnomAD. *Genet Med.* 2018;20(8):867-871.
30. Lynch SA, Crushell E, Lambert DM, *et al*. Catalogue of inherited disorders found among the Irish Traveller population. *J Med Genet.* 2018;55(4):233-239.
31. Oniya O, Neves K, Ahmed B, Konje JC. A review of the reproductive consequences of consanguinity. *Eur J Obstet Gynecol Reprod Biol.* 2019;232:87-96.
32. Khan N, Benson J, Macleod R, Kingston H. Developing and evaluating a culturally appropriate genetic service for consanguineou s South Asian families. *J Community Genet.* 2010;1(2):73-81.
33. Gitsels-van der Wal JT, Manniën J, Gitsels LA, *et al*. Prenatal screening for congenital anomalies: exploring midwives' perceptions of coun seling clients with religious backgrounds. *BMC Pregnancy Childbirth.* 2014;14:237.

34. Birmingham Women's Hospital. Enhanced Genetic Services Project Evaluation Report. Available from: https://www.phgfoundation.org/documents/376_1412153210.pdf accessed on 10th May 2020
35. Baig SM, Din MA, Hassan H, *et al*. Prevention of beta-thalassemia in a large Pakistani family through cascade testing. *Community Genet.* 2008;11(1):68-70.
36. Lord J, McMullan DJ, Eberhardt RY, *et al*. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. *Lancet.* 2019;393(10173):747-757
37. Jenkins LA, Deans ZC, Lewis C, Allen S. Delivering an accredited non-invasive prenatal diagnosis service for monogenic disorders and recommendations for best practice. *Prenatal Diagn.* 2018;38(1):44-51.
38. Sund KL, Zimmerman SL, Thomas C, *et al*. Regions of homozygosity identified by SNP microarray analysis aid in the diagnosis of autosomal recessive disease and incidentally detect parental blood relationships. *Genet Med.* 2013;15(1):70-8.

LEGENDS FOR FIGURES & TABLES:

Table 1 – Demographics and indication for referral (*=$p<0.05$ $^{\delta}$=initial testing performed based upon the presence of a fetal structural anomaly)

Table 2 - Anomaly subtypes and investigation up-take where recorded/applicable

Table 3 - Pregnancy outcome where recorded/applicable *Diagnostic test 'other' not included **Outcome 'miscarriage' not included

Figure 1 – Indication for referral to the prenatal genetic clinic and typical clinical pathway [CMA = Chromosome microarray; ES = Exome sequencing; MDT = Multi-disciplinary team] *Abnormal result refers to an abnormal CMA or ES/targeted testing result.

Supplementary Table 1 – All cases of genetic diagnoses in consanguineous couples [AR = Autosomal recessive; CMA = Chromosome microarray; DN = De novo; IUD = Intrauterine death; LB = Livebirth; NND = Neonatal Death; TOP = Termination of Pregnancy]

TABLES

	Consanguineous N=62 Mean (SD) or N(%)	Non-consanguineous N=218 Mean (SD) or N(%)
Maternal age (years)	29.2 (+/-4.9)	30.10 (+/-6.23)
Gestation (weeks)	23.1 (+/-6.0)	23.4 (+/-5.45)
Singleton pregnancy	62 (100)	215 (98.6)
Ethnicity		
Caucasian*	0 (0)	165 (75.7)
African-Caribbean	4 (6.5)	21 (9.6)
Chinese	0 (0)	1 (0.5)
South Asian*	53 (85.5)	30 (13.8)
Pakistani*	40 (64.5)	13 (6.0)
Bangladeshi*	10 (16.1)	4 (1.8)
Indian	3 (4.8)	13 (6.0)
Middle Eastern*	5 (8.1)	1 (0.5)
Parity*	1.7 (+/-1.4)	0.9 (+/-1.1)
Previous pregnancy loss		
Miscarriage	5 (8.1)	34 (15.6)
Perinatal death*	21 (33.9)	26 (11.9)
Termination	9 (14.5)	25 (11.5)
Interpreter required*	18 (29.0)	10 (4.6)
Indication for referral		
Sequence of anomalies	27 (44.0)	94 (43.1)
Recurrence of anomaly*	24 (38.7)	28 (12.8)
Previous anomaly which may have genetic basis	11 (17.8)	25 (11.5)
Abnormal karyotype/microarray result*$^{\delta}$	0	49 (22.5)
Other	0	22 (10.1)

Table 1

Variable	Sub-type	Group	N (%)	OR (95% CI)	p-value
Anomalies	Isolated	Consanguineous (N=49)	22 (44.9)	0.5 (0.3-1.0)	0.07
		Non-consanguineous (N=177)	107 (60.5)		
	Multi-system	Consanguineous (N=49)	27 (55.1)	1.9 (0.9-3.6)	0.07
		Non-consanguineous (N=177)	70 (39.5)		
Invasive test uptake		Consanguineous (N=50)	18 (36.0)	0.4 (0.2-0.7)	0.003
		Non-consanguineous (N=185)	113 (61.1)		
Autopsy		Consanguineous (N=35)	14 (40)	0.6 (0.3-1.4)	0.35
		Non-consanguineous (N=98)	50 (51)		
Decline follow-up/ investigation		Consanguineous (N=62)	10 (16.1)	10.3 (3.1-34.1)	0.001
		Non-consanguineous (N=218)	4 (1.8)		

Table 2

Variable	Sub-type	Group	N (%)	Odds ratio (95% CI)	p-value
Diagnosis obtained		Consanguineous (N=52)	14 (26.9)	0.3 (0.2-0.6)	0.001
		Non-consanguineous (N=171)	92 (53.8)		
Diagnostic test*	CMA/Karyotype	Consanguineous (N=12)	2 (16.7)	0.2 (0.04-0.9)	0.03
		Non-consanguineous (N=78)	41 (52.6)		
	Sequencing	Consanguineous (N=12)	10 (83.3)	5.6 (1.2-27.1)	0.03
		Non-consanguineous (N=78)	32 (41.0)		
Diagnosis timing	Postnatal	Consanguineous (N=14)	14 (100)	25.5 (1.5-439.9)	0.03
		Non-consanguineous (N=92)	49 (53.3)		
Pregnancy outcome**	Livebirth	Consanguineous (N=62)	26 (41.9)	0.6 (0.3-0.9)	0.04
		Non-consanguineous (N=218)	124 (56.9)		
	Perinatal death	Consanguineous (N=62)	22 (35.5)	3.6 (1.9-6.9)	0.0001
		Non-consanguineous (N=218)	29 (13.3)		
	Termination	Consanguineous (N=62)	14 (22.6)	0.7 (0.4-1.4)	0.33
		Non-consanguineous (N=218)	63 (28.9)		
Recurrence of structural anomaly in next pregnancy		Consanguineous (N=45)	8 (17.8)	3.9 (1.2-12.6)	0.02
		Non-consanguineous (N=120)	5 (4.2)		

Table 3