Evolution of a prenatal genetic clinic—A 10-year cohort study

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What is already known about this topic?

Prenatal genomic testing is developing at a significant pace. The use of a clinical multi-disciplinary team (including members with expertise in dysmorphology) to interpret results can optimise the chance of obtaining a unifying genetic diagnosis

What does this study add?

With use of a dedicated prenatal genetic clinic with a structured multi-disciplinary team approach, a unifying genetic diagnosis can be obtained in over 40% of cases reviewed prenatally with structural congenital anomalies

Data availability: The full anonymised, prospectively collected dataset is available from the corresponding author on request

ABSTRACT

OBJECTIVE (i) evaluate the proportion of women where a unifying genetic diagnosis was obtained following assessment of an observed pattern of fetal anomalies and; (ii) assess trends in genetic testing in a joint fetal-medicine genetic clinic.

METHOD Retrospective cohort study of all women attending the clinic. Outcomes included: (i) indication for referral; (ii) genetic test performed and; (iii) diagnoses obtained.

RESULTS From 2008 to 2019, 256 patients were referred and reviewed, of which 23% (n=59) were consanguineous. The main indication for referral was the observed pattern of fetal anomalies. Over 10 years, the number of patients reviewed increased from 11 to 35 per annum. A unifying genetic diagnosis was obtained in 43.2% (n=79/183), the majority of which were diagnosed prenatally (50.6% (n=40/79)). The main investigation(s) which was the ultimate diagnostic test was targeted gene panel sequencing 34.2% (n=27/79), with this and exome sequencing becoming the dominant genetic test by 2019. Pregnancies reviewed due to an abnormal karyotype or microarray decreased as an indication for referral during the study period (21.6% (n=16/74) 2008-2012 vs. 16.5% (n=30/182) in 2012-2019).

CONCLUSION A prenatal genetic clinic with a structured multi-disciplinary team approach may be successful in obtaining a unifying prenatal genetic diagnosis.

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INTRODUCTION

Congenital malformations complicate approximately 3% of pregnancies in the UK and just under half of these will have an underlying chromosomal (40%) or Mendelian ~~monogenic~~ (8.5%) cause which can be identified using current testing.[1,2] In the last decade, prenatal diagnosis has evolved at a significant pace with the introduction of high resolution, sub-microscopic chromosomal and single-gene testing strategies.[3,4] Establishing a prenatal joint fetal medicine and genetic service is a vital step in the provision of offering such testing with the need to strike a balance between good clinical skills and selection of the appropriate test. This will maximise the opportunity to identify the correct diagnosis and establish the risk of recurrence in a timely fashion.[5] Clinical geneticists and fetal medicine subspecialists with expertise in dysmorphology and prospective pattern recognition of ultrasound-detected fetal structural anomalies (FSAs) are important members of the team.[6] However, success relies on the additional skills provided by genomics laboratory staff, perinatal pathologists, genetic nurse counsellors and midwives. Implementation of such a multi-disciplinary team (MDT) approach can optimise counselling (pre and post-test), accurate phenotyping, the interpretation of chromosomal and Mendelian–variants in the era of molecular genetic testing.[7,8] Pregnancy poses a unique scenario in which clinical examination of the proband is limited to detailed, prenatal ultrasound to guide investigation. Identification of the fetal phenotype is vital and involves the detailed systematic examination of the proband (using high-resolution ultrasound and other tests such as in-utero magnetic resonance imaging (MRI)). Equally important is obtaining a family pedigree, evaluating the presence of consanguinity and any previously affected pregnancies. It is probable that there will be limitations in prenatal phenotyping and this may even alter with gestational age. The recognition of a fetal phenotype with high risk of

an underlying Mendelian aetiology influences the relatively short time period required for prospective testing in pregnancy.[6,9] Traditionally, testing and identification of a genetic aetiology has rested upon further postnatal investigation (usually by fetal post-mortem) in a prenatally identified anomaly.[10] This can be useful for targeting genetic analysis either postnatally or in a subsequent pregnancy, and to aid interpretation of any genetic findings. Going forward with the potential for prenatal exome and whole genome sequencing (ES and WGS), the selection of probands for investigation will become increasingly more common and require careful evaluation by an MDT review panel.[11,12] The objectives of this study were to:

(i) evaluate the proportion of probands (fetuses) where a unifying diagnosis was obtained following prospective assessment in the prenatal genetic clinic.

(ii) retrospectively assess trends of referral type and the use of new molecular genetic technologies over a ten-year period.

METHODS

Cohort sample

This was a retrospective examination of a prospectively collected cohort series of women/couples attending a combined fetal medicine and clinical genetic clinic at the Birmingham Women's and Children's NHS Foundation Trust between May 2008 and April 2019 (131 months). This regional tertiary prenatal centre serves a population of 5.5 million in the West Midlands, UK serving 17 separate obstetric centres and reviewing approximately 7500 fetal medicine patients per annum. The West Midlands Regional Genetic Service (WMRGS) has multiple clinical centres spanning the region, each with an assigned clinical geneticist and genetic counsellor, assessing approximately 8000 patients per annum. A significant proportion of prenatal genetic patients are seen and reviewed in such clinics with genetic MDT support by the central WMRGS hub at Birmingham Women's Hospital (BWH) and referrals coming from the corresponding fetal medicine centre. Work-up regarding the organisation of prenatal testing following a previous pregnancy where a genetic cause was identified or where parents are known carriers for a genetic disorder is performed by genetic counsellors with invasive testing or non-invasive prenatal diagnosis (NIPD) are offered at the corresponding fetal medicine centre and analysis performed centrally at the West Midlands Regional Genetic Laboratory.[13] NIPD is also an option prenatally in instances where an FGFR-3 related skeletal dysplasia is suspected. This study describes the central prenatal genetic clinic in the primary tertiary centre for this region where internal patients are referred directly or complex patients are externally referred within the West Midlands region and beyond. Criteria for referral to the clinic include women reviewed at the Birmingham Women's Hospital with; (i) an abnormal chromosomal or genetic result in an index or previous pregnancy requiring counselling or further input for patients where

testing has been performed; (ii) a personal or family history of a chromosomal or genetic disorder; (iii) a sequence of anomalies suggestive of a single gene disorder (which may present prenatally or following subsequent post-mortem) and; (iv) recurrence of a congenital anomaly. The current clinical pathway for women/couples attending this clinic are described in Figure 1. The MDT structure for this clinic evolved to include two fetal medicine consultants [FM and MDK], a clinical geneticist with expertise in dysmorphology [DW], a prenatal genetic clinical fellow, prenatal genetic midwife [LQJ], two genetic counsellors and two genetic scientists [SH and SA]. It also provided training for fetal medicine subspecialists. For the majority of the period examined, the clinic occurred monthly but from the beginning of 2019, it now runs twice a month and begins with an MDT meeting to discuss potential prenatal or postnatal testing options for pregnancies; along with a discussion of pre- and post-testing interpretation of any results. The perinatal post-mortem test results further inform results via a separate fetal pathology-genetics MDT held once per month where all relevant post-mortems performed in the West Midlands region are discussed [led by TM].

Patient pathway

Since 2008 at the fetal medicine centre and perinatal pathology service at Birmingham Women's & Children's Foundation Trust, conventional prenatal G-banding karyotype has been replaced by comparative genome hybridisation microarray assessment (CMA) preceded by quantitative fluorescent polymerase chain reaction (QF-PCR), targeting chromosomes 13,18,21 and the sex chromosomes. This is performed in the instance of any FSA or an elevated nuchal translucency (NT) >3.5mm. CMA was commenced initially, during the Birmingham BAC study and then the EACH (Evaluation of Array Comparative genomic

Hybridisation in prenatal diagnosis of fetal anomalies) research study before being introduced into standard clinical practice.[14,15] Recruitment into the PAGE (Prenatal Assessment of Exomes and Genomes) study commenced in 2014 and saw prenatal ES in fetuses (as part of a trio) identified with an FSA[16] It is anticipated that, such prenatal ES will be introduced more widely into clinical practice within the NHS as part of the new genomics test directory.[17] CMA testing is based upon an 8-plex platform of 60,000 60-mer oligonucleotides [Oxford Gene Technology (OGT) v3.0 Constitutional] and the results of our group's cohort have been described previously.[18] Approximately 367 CMAs are currently performed per annum (2018/9) within our genetics service with a pathogenic copy number variant (CNV) rate in the presence of any FSA (including elevated NT) of 6.8%.[18] Clinical ES using TruSight One Expand (Illumina) performed with trio analysis in Sapientia (Congenica) using a virtual panel of 1542 prenatally relevant developmental disorder associated genes (based upon the Deciphering Developmental Disorders (DDD) study, and as described in the PAGE study).[16,19]

Data collection

This descriptive cohort study included all patients who attended the joint fetal medicine/ genetic clinic during a ten-year period. Data was collected via the computerised fetal ultrasound reporting system Viewpoint 6® (GE, 2019) and online patient genetic databases. Subjects were excluded if there was not a suspected genetic reason for their visit. It was stated that a diagnosis was obtained if it had been identified by the time of data collection (September 2019). Due to the anonymised nature of the data and descriptive nature of the study it was deemed exempt from ethical approval. However, it was conducted within the Birmingham Women's and Children's NHS Foundation Trust Governance framework for

audit and was prospectively registered as such. The data presented is predominantly described using mean and range with calculation of p-values via Chi-Square testing where applicable.

RESULTS

Over 131 months, 275 patients were prospectively booked into the combined fetal-medicine genetic clinic for review and discussion. Nineteen women/couples (6.9%) declined the invitation with 256 women/couples undergoing review and attending the clinic. Of these, 16% (n=41) were also reviewed postnatally. The demographics of the attending cohort sample are demonstrated in Table 1.

Indication for referral and investigations.

The main indication for referral was a cluster of ultrasound anomalies that made clinicians suspicious of an underlying genetic or chromosomal aetiology [40.6% (n=104/256)], of which the commonest anomalies were multisystem in nature 56.7% (n=59/104), followed anomalies of the extremities/skeleton 21.2% (n=22/104). The second most common indication for referral was the recurrence of an FSA. In this sub-cohort, 46.4% (n=26/56) of couples referred were consanguineous [Figure 2]. When an ultrasound-detected FSA was documented (n=199), it was of a multisystem nature in n=86 cases (43.2%) and in cases of an isolated anomaly n=113 (56.8%), the most commonly affected organ systems were those of the brain n=54 (47.8%) and heart n=51 (45.1%). Of this sub-cohort, where FSAs were prospectively identified, prenatal invasive testing was performed in many cases; with 61.5% (n=83/135) undergoing amniocentesis, 26.7% (n=36/135) chorionic villous sampling and; 11.8% (16/135) fetal blood sampling. Fetal MRI was additionally performed in 17.2%

(n=44/256). The median number of patients reviewed per annum was 22 (range 11-35), gradually increasing each year, with the greatest number of patients seen in 2017-2018 (n=35).

Outcome

Where applicable, in cases of FSA, a definitive clinical or genetic diagnosis was eventually reached in 47.7% (n=95/199) of cases. In instances where a non-genetic clinical diagnosis was made, this was based upon neonatal clinical or post-mortem examination by a clinical geneticist (n=16), with examples included Asphyxiating Thoracic Dystrophy, Fryns syndrome, OEIS (Omphalocele-Exstrophy of the cloaca- Imperforate anus-Spine complex), Isolated Femoral Hypoplasia and VACTERL (Vertebral defects-Anal atresia-Cardiac defects-Tracheo-esophageal fistula-Renal anomalies-limb anomalies) association. In those where a unifying genetic diagnosis (chromosomal or single gene) was made (43.2% (n=79/183)), this was based upon testing initiated following detection of a newly identified or recurrent FSA on ultrasound scan (including elevated NT) when no testing had previously been performed. These genetic diagnoses were predominantly achieved prenatally (50.6% (n=40/79)). The overall median time taken to achieve the diagnosis was 28 (range 3-3285) days, predominantly due to the range of testing being offered (some of which wasn't available when patients were seen at the start of the study period) and the prolonged timeframe of ES when initially introduced in the research setting (median time for single gene diagnosis 49 (range 12-3285) days). All positive chromosomal and genetic results are described in Supplementary tables 1-3. The predominant ultimate diagnostic test within our cohort in instances of FSA identified in a pregnancy, which was undergoing genetic investigation for the first time, was single gene/targeted panel testing or testing via other modalities which

were not ES 34.2% (n=27/79), followed by karyotype 26.6% (n=21/79). Fetal outcomes and diagnostic yield are demonstrated in Table 2. Rates of pregnancy loss of patients reviewed in the clinic overall were high (44.9% (n=115)), usually because of couples opting for termination of pregnancy (25.4% (n=65)). Rates of survival beyond the neonatal period for (i) causative abnormal QF-PCR/Karyotype, CMA and single gene disorders were 19.0% (n=4/21); 31.6% (n=6/19) and; 25.6% (n=10/39) respectively and not significantly different between groups (p=0.66).

Chromosomal and Genetic Diagnoses

The commonest abnormalities identified within each type of testing were:

(i) QF-PCR/karyotype -monosomy X (n=7/21);

(ii) CMA - Di George 22q.11.2 microdeletion (n=4/19);

(iii) single gene disorders - Beckwith-Wiedemann syndrome (n=5/39) and Noonan Syndrome (n=3/39)

Assessing the inheritance patterns of causative single gene mutations, most were *de novo* and inherited in an autosomal fashion dominant 48.7%; (n=19/39). Of note, as the aforementioned abnormalities (i)-(iii) represented pregnancies referred to a specialist prenatal genetic clinic, then there was bias in relation to some of the groups e.g. group (i) was is lacking in straightforward trisomy 13, 18 and 21 cases which are unlikely to be referred into the clinic as they are typically managed within the fetal medicine or obstetric department. In the year 2018-2019 at BWH, of the 168 invasive prenatal tests performed in the fetal medicine unit for fetal anomaly (including elevated NT) there were n=48 (28.6%) abnormal QF-PCR or CMA results. Of these there were n=6 cases of Turner syndrome, n=1 Klinefelter's syndrome, n=1 48,XXX+21 and n=4 CNVs which were not reviewed at the

prenatal genetic clinic but managed by the fetal medicine consultant with or without input from the genetic counsellor, with the remainder of cases representing common Trisomies 13, 18 or 21.

Trends during the ten-year study period.

This was assessed by comparing the eras of 2008-2011 (karyotype/QF-PCR) vs. 2011-2014 (CMA) vs. 2014-2019 (ES). Where applicable there was no difference between predesignated cohort eras in relation to achieving a unifying genetic diagnosis; 31.7% (n=13/41); 29.1% (n=16/55) and; 31.3% (n=50/160) respectively p=0.95. There was a change in trend of the ultimate diagnostic test, with ES and targeted gene testing eventually overtaking QF-PCR/karyotype [Figure 3]. Mean time taken to obtain a diagnosis reduced throughout the three eras from 601.6 to 154.4 to 139.7 days respectively. In instances where an abnormal karyotype/CMA was the indication for referral comparing 2008-2012 vs. 2012-2019 there was a trend toward a reduction in referrals for this indication 21.6% (n=16/74) vs. 16.5% (n=30/182) but this was not significant (p=0.40).

DISCUSSION

This ten-year retrospective cohort study describes the evolution of a joint fetal medicine/ genetic clinic at a tertiary centre in England. During this period, a unifying genetic diagnosis was obtained in over 40% of referred cases and testing for single gene disorders (either targeted or by ES) overtook karyotype/CMA as the ultimate diagnostic test. A corresponding reduction in time taken to obtain a diagnosis was also demonstrated. It displays the growing demand for this service with parents wishing to know why their fetus/child was affected by a congenital malformation, the potential long-term prognosis and the risk of recurrence in any future pregnancies. In this cohort, it is recognised that there was a relatively high prevalence of parental consanguinity.

The translation of research-based investigation into routine clinical practice is clearly demonstrated within this cohort by the shifting trend towards ES and single gene testing as the most common diagnostic test increasingly represented through this specialist clinic. This provides an example of how a leading international prenatal genetic centre which was instrumental in the introduction of prenatal CMA and ES manages such patients. Such translation is traditionally known to be challenging and at times protracted. However, the continued MDT and genomics laboratory support which had already been established

through a research pathway; in addition to prompt protocol design for CMA and ES, with added support from the National Health Service, has optimised the success of this service.[20,21] The changes seen in the trends of testing take nothing away from the value of QF-PCR or CMA nor do they compare results of Mendelian testing to them, but represent that these tests are increasingly being offered and followed up within the other centres and that patients with fetuses which have anomalies more representative of single gene disorders are being referred to this specialised central service as this testing becomes integrated into clinical care.

One in four of the population of Birmingham are of South Asian ethnicity and consanguinity as high as 50% in this group.[22,23] This explains the significant proportion of consanguinity seen in this study (23%) and the high number of genetic syndromes which were recessive in nature (39%).[24] It has been demonstrated that since 2014 in the United States prenatal genetic testing has significantly increased and notably in relation to multi-gene panel testing this accounts for the largest proportion of money spent in the field of genetic testing overall. This supports the trend visible from our own study and reflecting the initiation of ES seen internationally.[25] It is interesting that despite the introduction of ES, in instances where a diagnosis had been achieved was more common with targeted testing as opposed to ES (32.1% vs. 16.7%), potentially supporting an ES targeted panel approach moving forward.[11] However, prenatal ES is in its infancy and case selection and bias may well account for this observation.

In many instances a diagnosis was not achieved until the postnatal period. This highlights the additional benefit of obtaining a postnatal phenotype by external examination and post-

mortem examination after a prenatal phenotype in guiding subsequent testing and interpretation of variants.[26] It is recognised, that parents are often reluctant to allow full, conventional post-mortem examination of their baby. For this reason, there will be a need to consider targeted post-mortem examination taking into account prenatal full imaging and prospective genetic tests.[27]

Instances of referral of couples where there was an abnormal karyotype or CMA result in their fetus tended to reduce with time, which may be explained by the fact that genetic counsellors and fetal medicine sub-specialists are now more comfortable with counselling patients with regards such findings, meaning they no longer need to be referred to specialist prenatal genetic clinics. However, it may also be because of falling rate of variants of uncertain significance.[18,28] In this study the duration of time to diagnosis time for molecular genetic testing is influenced by many factors. Primarily, the study period involved the research assessment of both CMA and ES.[15,16] Of particular note, was the fact that the PAGE study only revealed causative pathologic variant results after completion of the pregnancy (as set out in the initial protocol). In addition, this cohort is a mixture of prenatal and postnatal cases with varying prioritisation and timing of molecular genetic testing. It is likely though, that in future, improved variant analysis and the 'pipeline' assessing phenotype/genotype match will reduce turn clinical around time to <20 days. In our study, most patients referred with a sequence of anomalies suggestive of a single gene disorder had multi-system anomalies, as it is understood that these have the greatest diagnostic yield with ES.[16] It is anticipated that as we come to understand more about the diagnostic yield of ES in isolated prenatally detected anomalies e.g. cardiac and renal, more cases will be referred to a genomic MDT and hence pick up of related disorders such as Alagille

syndrome or infantile polycystic kidney disease will be greater. Further research and education will be required to optimise such triaging and case selection.[29]

Strengths of this study lie in its novelty as it is, to our knowledge, one of the first studies in which prospective cohort study has been retrospectively analysed to describe the workflow and patient population of a prenatal genetic clinic. Additionally, follow-up of all patients was completed as of 2019 and the core staff running the service (M.D.K. & D.W.) remained stable throughout the decade, which optimised continuity.

The main limitation was the fact that establishment of a diagnosis could potentially occur up to a ten-year period from when the patient was first reviewed. The reason for the protracted time period (up to 3285 days) was because CMA and ES wasn't actually available during the earlier era of the cohort, and was made available to patients as part of a research study through much of the audit period. Hence the prolonged time to diagnosis is a result of multiple factors. This explains why there was no difference in diagnostic yields over time as cases seen more recently have had a limited time to traverse the so-called *'diagnostic odyssey'*. By the nature of assessment of the specialist prenatal genetic clinic only this introduces an element of ascertainment bias and only touches the surface in relation to prenatal services and testing offered within the West Midlands region as a whole, however this assessment was beyond the scope of the overall study objective. Over the decade time to reaching a diagnosis reduced, reflecting the introduction of CMA and ES. As there was a disproportionately high number of consanguineous patients compared to other regions in the UK, this may limit the generalisability of findings.[30]

Moving forward as demand for a prenatal genetic service grows, our tertiary centre is one of the lead contributors in supporting development of the prenatal service nationally through NHS Genomic Medicine Service.[21] This combined with future development of clinical guidelines for the application of prenatal ES will both consolidate and develop the service. Targets for the future will be to reduce turnaround times for genetic testing and to develop targeted genomic panels (e.g. PanelApp)[31] with the aim to optimise diagnostic yield as well as provide genetic diagnoses prenatally to aid in guiding the management of an affected pregnancy. For couples with a 1 in 4 recurrence risk of a rare autosomal recessive disorder, and different parental variants, it may be possible to design a bespoke NIPD assay for the paternal pathogenic variant to offer paternal exclusion testing in subsequent pregnancies.[13,32] This is a service which is being offered within our centre and for which results are pending publication. An economic evaluation of the aforementioned services would be useful in determining overall benefit, although in line with Moore's law, the cost of genetic testing and notably ES should reduce with time.[29,33]

CONCLUSION

This cohort study demonstrates the experience of a joint fetal medicine / clinical genetic clinic over the last decade with a move to molecular genomic technologies and provides an example of how a prenatal genetic service is provided. With an appropriate MDT pathway in over 40% of cases where patients were predominantly seen in the setting of congenital anomaly, a diagnosis was obtained. With growing demand for prenatal genetic diagnosis, national and international expansion of this service is required backed by clinical guidelines and economic evaluation.

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TABLE AND FIGURE LEGENDS

Table 1: Demographic characteristics of attending population (N=256)

Table 2 Outcomes of subjects attending the fetal medicine genetic clinic [NIPT=Non-invasive prenatal testing; QF-PCR = Quantitative fluorescence-polymerase chain reaction]

Figure 1 Fetal medicine-genetic clinic clinical pathway [CMA = Chromosome microarray; MDT = multidisciplinary team; QF-PCR = Quantitative fluorescence-polymerase chain reaction]

Figure 2 Indication for referral to fetal medicine genetic clinic

Figure 3 Trend in genetic test which resulted in a diagnosis [QF-PCR = Quantitative fluorescence-polymerase chain reaction]