Recent Advances in Paediatrics



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Chapter 4

Prenatal screening and diagnosis of genetic defects

Tara Giacchino, Ranjit Akolekar

INTRODUCTION

Prenatal screening and diagnoses have rapidly evolved over the past few decades in parallel with advances in prenatal ultrasound techniques and improvements in genetic investigations. The aim of prenatal diagnosis is to provide women and their families with accurate information about their pregnancy regarding the genetic health so that they can make appropriate management plans based on these results. Depending on the nature of the genetic diagnosis, the management options available to a family and their clinical team include accurate results that can allow for close antenatal monitoring, specialist consultations with fetal medicine and genetics team, planning and preparation for optimal timing, mode and place of birth and need for specialist neonatal care. Also in some pregnancies, the option of considering a termination of pregnancy if the genetic defect is associated with substantial risk of perinatal death or severe handicap; the latter is subject to medical and legal guidelines that vary considerably among different countries. The knowledge of accurate prenatal diagnosis allows not just for effective management of the current pregnancy but provides information that can help in determining recurrence risks and management of future pregnancies.

CHROMOSOMAL AND GENETIC ABNORMALITIES

Chromosomal and genetic abnormalities can be broadly divided into those that are numerical chromosomal abnormalities such as aneuploidies (e.g. trisomy or monosomy), those associated with loss or gain of genetic material such as deletions or duplications and those associated with change in a nucleotide base change such as DNA mutations. Genetic abnormalities can also be classified as those that are sporadic occurrences, i.e. that occur in a de novo fashion or those that are inherited from parents. Common examples of sporadic occurrences of genetic defects include primary trisomy or monosomy and

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Table 4.1 Common types of chromosomal/genetic defects

Defect	Explanation	Examples
De novo or sporadic defects		
Primary trisomy	Whole additional chromosome	Down's, Edward's and Patau's syndrome
Primary monosomy	Missing entire chromosome	Turner's syndrome
Triploidy	Whole extra set of chromosomes	Digynic or Diandric triploidy
Deletion or duplication	Part of a chromosome missing or duplicated	DiGeorge, Cri Du Chat and William's syndrome
Single gene mutation	DNA mutation in a single gene	Cornelia De Lange's syndrome
Chromosome re-arrangements	Isochromosome, marker chromosomes	Pallister–Killian's syndrome
Inherited defects		
Secondary trisomy	Partial additional chromosome	Unbalanced translocation
Secondary monosomy	Partial missing chromosome	Unbalanced translocation
Deletion or duplication	Part of a chromosome missing or duplicated (as above)	Unbalanced translocation (as above)
Single gene defects		
Autosomal dominant	Only one abnormal copy required for defect to express	Huntington's chorea
Autosomal recessive	Both copies abnormal for defect to express	Cystic fibrosis
Sex-linked	Defect on X-chromosome in 23rd pair	Duchenne muscular dystrophy

deletions or duplications of parts of chromosomes whereas those that are inherited from parents include secondary trisomy or monosomy such as those inherited from parents carrying balanced chromosomal translocations when they become unbalanced and single gene disorders, i.e. DNA mutations those that are inherited from parents in a Mendelian fashion (e.g. recessive or dominant genetic defects, either autosomal or sex-linked) [1,2] (**Table 4.1**).

PRENATAL SCREENING FOR CHROMOSOMAL/GENETIC DEFECTS

Maternal risk factor-based screening

The most important risk factor associated with chromosomal abnormalities such as trisomy is maternal age. There is considerable evidence suggesting that the risk for fetal trisomies 13, 18 and 21, increases with maternal age. For example, the maternal age-related risk for trisomy-21, -18 and -13 at 12 weeks for a maternal age of 20 years is about

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1 in 1,000, 1 in 2,500 and 1 in 8,000 whereas the same risks for the same gestation for a maternal age of 35 years is 1 in 250, 1 in 600 and 1 in 1,800 [3–5]. In contrast, the risk for other chromosomal abnormalities such as Turner's syndrome and 'triploidy' is unrelated to maternal age; the prevalence of these defects at 12 weeks is about 1 in 1,500 and 1 in 2,000. Maternal age was the method of screening in the 1970s and women over the age of 35 years, which constituted about 5% of the population at the time, were defined as screen positive and were offered further diagnostic testing for trisomy-21 with a detection rate (DR) of 30% [3–5].

Serum-based screening

In the late 1980s and early 1990s, several studies demonstrated that in pregnancies with fetal trisomy-21 there are altered maternal serum concentrations of various biochemical markers, including increased free β-human chorionic gonadotropic (hCG) and inhibin A and decreased alpha-feto protein (AFP) and unconjugated oestriol 3 (uE3) [6–11]. These biochemical changes were combined with maternal age to develop the double test (hCG and AFP), triple test (hCG, AFP, and uE3) and the quadruple test (hCG, inhibin A, AFP, and uE3). Screening by this approach was superior to that of maternal age alone with DR of 50–70% at FPR of 5% [12]. However, these serum screening tests, i.e. triple, and quadruple tests were offered in the second trimester of pregnancy. As the advances occurred in fetal medicine, screening moved to the first trimester and it was realised that in pregnancies with fetal trisomies, there were significant alterations in concentrations of serum pregnancy associated plasma protein-A (PAPP-A) and free β-hCG in the first trimester of pregnancy [13,14]. The DR of trisomy-21 by first trimester biochemical markers was 60% for a false positive rate (FPR) of 5% [3].

Ultrasound-based screening

First trimester

An important milestone in prenatal screening was brought about by the introduction of ultrasound measurement of nuchal translucency (NT) at the first trimester 11–14-week scan. The seminal publication of the association of increased fetal NT thickness in pregnancies with trisomy-21 in 1992 and in the subsequent years demonstrated that a high proportion of affected pregnancies can be identified by ultrasound assessment of the fetus and measurement of fetal NT in first trimester [15–17]. For a FPR of 5%, screening by fetal NT thickness alone identifies about 75–80% of affected pregnancies. In addition to fetal NT thickness, other sensitive ultrasound markers of fetal trisomies at 11–13 weeks' scan include absence of fetal nasal bone, increased impedance to flow in fetal ductus venosus and tricuspid regurgitation, which are observed in about 60, 65, and 55% of pregnancies with trisomy-21, respectively [3,18–20].

Second trimester

A detailed ultrasound scan carried out in the second trimester around 20 weeks allows for examination of fetal anatomy and genetic markers associated with fetal chromosomal and genetic defects. For example, trisomy-21 is associated with ventriculomegaly, nasal hypoplasia, nuchal oedema, cardiac defects, duodenal atresia and echogenic bowel, mild hydronephrosis, shortening of the femur and humerus. Similarly, trisomy-13 or -18 can be associated with brain abnormalities, facial cleft, micrognathia, nuchal oedema,

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heart defects, diaphragmatic hernia, exomphalos, single umbilical artery, renal defects, echogenic bowel, myelomeningocele, growth restriction and shortening of the limbs. The likelihood of association with fetal trisomy-21, given the presence of these markers was reported in a recent meta-analysis [21] (**Table 4.2**).

Combined screening

In the 1990s, aneuploidy screening shifted to the first trimester with the 'Combined' test which uses ultrasound measurement of fetal NT together with maternal serum concentration of the placental proteins, free β-hCG and PAPP-A [3,15–17]. This combined test has a DR of 90% with FPR of 5% [3,17]. When combined screening is carried out with a combination of maternal age, fetal NT thickness, maternal serum free β-hCG and PAPP-A along with the additional ultrasound markers such as nasal bone, tricuspid valve and ductus venosus assessment, the DR can be improved to 96% for a FPR of 3% [22–24] (**Table 4.3**). The use of these additional ultrasound markers can be used in universal screening for all pregnancies but can also be used in a contingent screening policy whereby universal

Table 4.2 Likelihood ratios of ultrasound markers with fetal trisomy-21 [21]

Marker	Positive LR	Negative LR	LR isolated marker
Intra-cardiac echogenic focus	5.85	0.80	0.95
Ventriculomegaly	25.78	0.94	3.57
Increased nuchal fold	19.18	0.80	3.12
Echogenic bowel	11.44	0.90	1.65
Mild hydronephrosis	7.77	0.92	1.10
Short humerus	4.81	0.74	0.78
Short femur	3.72	0.80	0.61
Aberrant right subclavian artery	21.48	0.71	3.94
Absent or hypoplastic nasal bone	23.26	0.46	6.58

(LR, likelihood ratio)

Table 4.3. Performance of different methods of screening for trisomy-21 [3]

Method of screening	DR (%)	FPR (%)
Maternal age	30	5
Maternal age + fetal NT	75–80	5
Maternal age + fetal NT + serum free β-hCG and PAPP-A (combined screening)	85–95	5
Combined screening + nasal bone + tricuspid flow + ductus venosus flow	93–96	2.5

(DR, detection rate; FPR, false positive rate; hCG, human chorionic gonadotropin; NT, nuchal translucency; PAPP-A, pregnancy-associated plasma protein)

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screening is carried out using maternal age, fetal NT and serum biochemistry and those with a high-risk result of <1 in 50 can be offered further invasive testing, those with a low risk of <1:1,000 are reassured and those in the intermediate risk group of 1 in 51 to 1 in 1,000 are offered further specialist ultrasound assessment with these ultrasound markers [3,25].

DNA-based screening

In the late 1990s, it was discovered that free fetal DNA can be identified in maternal blood [26,27]. This cell-free (cf)-DNA in maternal plasma is a mixture of DNA fragments belonging to both the mother and fetus. The proportion of fetal to total cfDNA, referred to as fetal fraction is about 10% [28]. Recent advances in genetic technologies such as digital polymerase chain reaction (PCR), massively parallel sequencing and single nucleotide polymorphism (SNP) based methods have made it feasible to quantify these small increases in fetal cfDNA amount in trisomic pregnancies [29–31]. There have been several studies published in the last decade which demonstrate effectiveness of screening for fetal trisomies using the cfDNA. A recent meta-analysis demonstrated that in screening for trisomy-21, the weighted pooled DR and FPR were 99.7% and 0.04%, respectively. Similarly, for trisomy-13 and -18, the DR were 99.0% and 97.9%, respectively with corresponding FPR of 0.04% and 0.04%, respectively [32,33].

PRENATAL DIAGNOSIS FOR CHROMOSOMAL/GENETIC DEFECTS

Invasive prenatal diagnostic tests

Amniocentesis and chorionic villus sampling (CVS) are commonly performed procedures for invasive prenatal diagnosis. Women who are deemed to be at an increased risk for chromosomal abnormalities or those with a family history of an affected pregnancy are offered these diagnostic tests for further investigation. The aim is to obtain fetal DNA either from the placental (CVS) or the amniotic fluid (amniocentesis). These procedures are relatively safe with recent cohort studies and systemic reviews demonstrating that in pregnancies undergoing these invasive procedures, the procedure-related risk of pregnancy loss of about 0.3–0.5% [34,35]. CVS is generally preferred as it allows prenatal diagnosis at an earlier gestation and therefore provides reassurance if the results are normal. Furthermore, if the results are abnormal, CVS facilitates decision making at an earlier gestation, compared to amniocentesis, as CVS can be carried out at or after 11 weeks' gestation whilst amniocentesis can be carried out at or after 15 weeks' gestation.

Laboratory genetic tests

Once genetic material is obtained for further laboratory investigation following a CVS or an amniocentesis, the tests available depend on the clinical indication for prenatal diagnosis. The common laboratory investigations include quantitative fluorescence polymerase chain reaction (QF-PCR), fluorescent in-situ hybridisation (FISH), karyotyping and comparative genomic hybridisation (CGH) array or SNP array, whole exome sequencing (WES) and molecular genetic testing for DNA mutations.

QF-PCR amplifies chromosome-specific DNA sequences or short tandem repeats and uses fluorescent primers to identify and quantify the amplified sequences as 'peak

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areas' on automated machines. Normal heterozygous individuals demonstrate two peak areas for each chromosome while those with trisomies will show an extra peak or an imbalanced peak ratio [36]. QF-PCR also provides rapid result within 3 days and can only be used to detect the common aneuploidies (T21, T13, and T18), sex chromosome abnormalities and triploidies.

FISH involves preparing fluorescent-labelled 'probes' or short sequences of single-stranded DNA that match up with the gene mutation being investigated for and bridges the gap between cytogenetics and molecular DNA testing. FISH can be done if early diagnosis is needed as the result is known in 24 hours; however, a positive result obtained by FISH needs to be reconfirmed by micro-array or karyotype [37,38]. FISH is advantageous as it detects subtle changes in chromosomes like duplications or deletions and can be done to interphase nuclei of non-mitotic cells. Therefore, the long process of cell culture is not needed, making it an ideal test in pre-implantation genetic diagnosis as it is quick [39]. Both FISH and QF-PCR need confirmation from the final karyotype; QF-PCR is often preferred over FISH as it requires few cells, is cheaper and as an automated machine is used, many samples can run concurrently and quickly.

Fetal karyotype with G-banding is the gold standard cytogenetic test for prenatal diagnosis of chromosomal abnormalities or aneuploidy and involves looking at the number as well as the structure or characteristic banding pattern of the 23 chromosome pairs. G-banding involves the use of Giemsa staining to divide a chromosome into regions, bands and sub-bands to detect abnormalities or re-arrangements like deletions, translocations, insertions or inversions. The sensitivity and specificity of this testing is nearly 99%, except for cases where confined placental mosaicism is present, and the fetal DNA sample was obtained by CVS [40].

Micro-array-based comparative genomic hybridisation (array CGH) directly compares DNA from two genomes, i.e. the patient and the control or reference which are uniquely fluorescently labelled and co-hybridised on a solid microscope slide with hundreds or thousands of immobilised DNA fragments or 'targets'. The advantage of this test with several overlapping targets, over FISH or other molecular cytogenetic tests is the detection of simultaneous DNA mutations at different loci in a given genome including deletions, duplications, or copy number imbalances [41,42]. In comparison, the highest resolution for standard karyotyping by G-banding is 3 Mb, for FISH is 1–2 Mb with the best resolution of 1 Kb obtained by aCGH. It can be considered as reliable as conventional karyotyping at diagnosing aneuploidy and unbalanced mutations. The limitations of chromosomal microarray include inability to detect single nucleotide mutations, abnormalities associated with balanced translocations, mosaicism and triploidy [43,44]. This led to another type of test known as SNPs array which involves the analysis of small segments of DNA affecting one nucleotide base which can detect small abnormalities including triploidy [45].

Whole exome sequencing (WES) has been introduced to better prenatal diagnosis when structural abnormalities have been confirmed on ultrasound or if there is a family history of consanguinity or similar fetal abnormalities without a genetic diagnosis. WES detects aberrations in the protein coding region of the genome and any changes to the norm are known as variants which can be categorised as pathogenic, likely pathogenic, benign, likely benign or of unknown significance. The improved diagnostic yield ranges from 10 to 50% and is case dependant and highly dependent on the indication for WES [46].

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CONCLUSION

- Common genetic and chromosomal defects include aneuploidies, chromosomal or genetic deletions or duplications, chromosome re-arrangements and single nucleotide changes.
- Chromosomal and genetic abnormalities can either occur in a sporadic or de novo fashion with no significant implications for future pregnancies or could be inherited from parents who are carriers of balanced chromosome re-arrangements or single gene disorders.
- The management of pregnancies at high-risk of chromosomal or genetic defects should be undertaken with specialists in fetal medicine and clinical genetics.
- The current method of prenatal screening for fetal trisomies is combined screening in the first trimester which estimates an individual patient-specific risk based on maternal age, fetal NT thickness and serum biochemistry (free β-hCG and PAPP-A). Additional ultrasound markers in the first trimester such as nasal bone, tricuspid and ductus venosus flow, improve DR and reduce FPR.
- cfDNA-based screening for fetal trisomies is highly accurate and identifies >99% of affected pregnancies at a low FPR of <0.1%.
- Common tests to obtain samples for prenatal diagnosis include CVS and amniocentesis, which can be carried out after 11 and 15 weeks, respectively.
- QF-PCR and FISH can be used for rapid prenatal diagnosis of aneuploidies with results available in 24–48 hours.
- Chromosome re-arrangements including deletions and duplications can be effectively identified using G-banding karyotype and micro-array-based techniques such as CGH and SNP array. The micro-array-based techniques have a higher resolution and are better in detecting smaller genetic changes.

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Recent Advances in Paediatrics

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Recent Advances in Paediatrics-29 features an outstanding collection of articles relevant to paediatricians and health professionals working with children and adolescents across the world.

This book reflects the changing landscape in paediatrics, with a significant emphasis on adolescent health, both physical and mental referencing the role of technology and innovations such as conversational AI and ChatGPT in improving outcomes.

Other topics include prenatal screening and diagnosis of genetic defects, advances in neonatal care, a systematic approach towards orthopaedic management of cerebral palsy, bone health and osteoporosis, as well as advances in surgery and urology.

We have included an emphasis on "safer care for sick children" with the role of safety checklists and escalation of care using hub and spoke models. Implementing safety checklists universally for procedures could mean doctors and nurses moving across hospitals (or even continents) can provide the same high standards of care.

The book will undoubtedly be a compelling read for medical students as it covers aspects of paediatrics often not covered in conventional textbooks and may inspire them to choose a career in Paediatrics.

Finally, some aspects of this book including the section on adolescent health, technology as well as improving safety will be relevant to parents, whose expertise in their own children is always one of the most valuable resources for paediatricians!

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