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A STUDENT'S PERSPECTIVE: DOWN SYNDROME, ITS GENETIC INHERITANCE, KARYOTYPE AND PREVENTION

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ABSTRACT
Down syndrome (Trisomy 21) is the most common chromosomal disorder and a leading genetic cause of intellectual disability worldwide. In India, the situation is compounded by late diagnosis, limited access to universal prenatal screening, and lack of awareness regarding genetic counseling. Early detection and informed reproductive choices are essential to reduce the social, emotional, and economic impact on families. The present study deals with prenatal genetic screening & chromosomal testing perceived during the internship (first author) as important healthcare measures for prevention of the birth of Down syndrome in a family.
The significant role of maternal biochemical screening, ultrasonography, NIPS, and confirmatory diagnostic tests is highlighted through a retrospective analysis of 3 high- risk pregnant women. The genetic tests included dual/quadruple biochemical markers, detailed fetal anomaly scan, NIPS (wherever possible), and confirmatory karyotype with FISH from amniotic fluid. Pre-test and post-test genetic counseling was provided to all 3 couples. Out of 3 high-risk pregnancies, advanced maternal age was in one case only & age ranged from 26-36 years. Two cases with positive dual/quadruple screening had normal karyotype on amniocentesis, highlighting the false-positive rate of screening. One case with abnormal USG [absent nasal bone, NT 4.0mm] and very high risk [1:9] in biochemical screening was confirmed as Trisomy 21 and opted for termination. None of the couples had undergone pre-conception carrier screening.
Down syndrome continues to be the predominant chromosomal abnormality with ID in India. While screening tests are valuable for risk stratification, confirmatory testing by karyotype and FISH remains essential. Making universal prenatal screening mandatory, integrating genetic counseling at primary healthcare level, and ensuring affordable access to NIPS and prenatal diagnostic services are emphasized as important factors to reduce the birth prevalence and burden of Down syndrome in India..

KEYWORDS: Down syndrome, Karyotype, Chromosomes, Inheritance, Prevention

1. INTRODUCTION

Genetics is the study of inheritance which occurs due to genetic material- DNA, being passed from parents to their offspring. It also includes the study of hereditary factors and the ways in which they express during the development and life of an individual. Genetics is a vast field consisting of several sub-branches like clinical genetics, cytogenetics, biochemical genetics & molecular genetics (1).
The present paper deals with cytogenetic & chromosomal testing. It is a student's perspective about 'Down syndrome'-a most common chromosomal genetic disorder causing intellectual disability (ID) in a child. It was developed during the internship (first author) at the Genetic Healthcare Laboratory & Genetic Counseling Centre. The genetic inheritance, diagnostic chromosomal testing, and prevention of the birth of Down syndrome in a family was learnt.
Over a period of time, since the discovery of a DNA molecule as a blue-print of human in 1952, the understanding of genes, their functions & abnormalities in their coding signals for protein formation has tremendously increased in the past few decades. Advanced research & genetic technology has opened new doors in laboratory diagnostic technology to identify genetic conditions & their prevention as well. One such genetic test is a 'Karyotype' test which is developed to detect normal and abnormal chromosomal patterns under the microscope to diagnose the genetic syndromes, including Down Syndrome, the most common chromosomal abnormality, also referred as Trisomy 21, due to extra chromosome 21.
Based on various biochemical & ultrasonography tests performed during pregnancy for the wellbeing of the unborn child (fetus), the high-risk for birth of Down syndrome can be predicted. Further prenatal chromosomal testing allows confirmation and future decision making is possible for the couple who may be showing 'high-risk' for Down Syndrome birth.
Thus, it is learnt that detection of birth of Down syndrome can be achieved through appropriate genetic testing during pregnancy and reducing genetic impact in terms of ID in the Indian population, similar to the approach that is presently being conducted in the developed countries.

REVIEW OF LITERATURE

The following literature reviews overall relevant Down syndrome features, its chromosomal abnormality, the mechanism, karyotype testing essential for diagnosis of the affected patient and also pregnancy-related screening tests for prevention in brief, to understand and appreciate the significance of this study

Cytogenetics & Chromosomes:

Cytogenetics is a branch of genetics which involves study of chromosomes and chromosomal abnormalities with respect to its structure, number, location and function. Abnormalities in the structure or number of chromosomes lead to several genetic disorders like aneuploidy (2).

Chromosomes are thread-like DNA structure which are tightly packaged within the nucleus. DNA is coiled around proteins called histones, which provide structural support. Chromosomes help to ensure that DNA is replicated and distributed appropriately during cell division. Each chromosome has a centromere which divides chromosomes into two sections- the p(short) arm and the q (long) arm. The centromere is located at the cell's constriction point, which may or may not be the center of the chromosomes (3).

Morphologically chromosomes can be observed in the karyotype and are classified according to the position of the centromere, described below and illustrated in Fig.1 -

- If centromere is located centrally, the chromosome is meta-centric.
- If centromere is located near one end, chromosome is acrocentric.
- If the centromere is in an intermediate position the chromosome is sub- metacentric
- If centromere is terminally located the chromosome is telocentric.

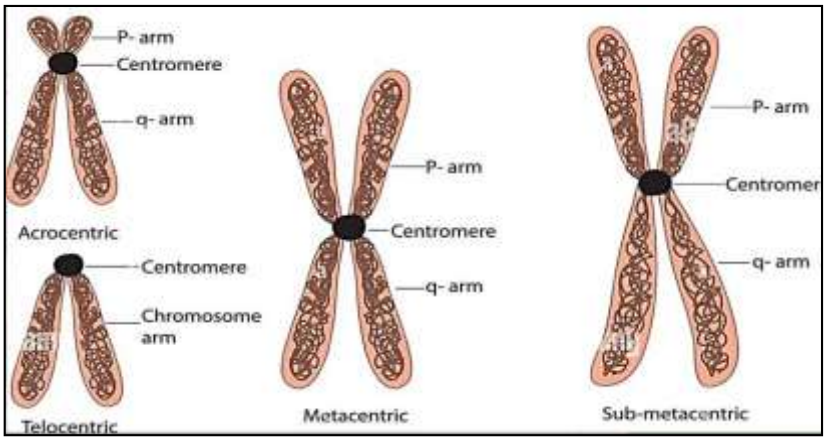

Fig.1: Morphology of chromosomes with respect to centromere, p-arm & q-arm.

Human Chromosomes - Humans have 46 chromosomes in 23 pairs, out of which 44 are autosomes and two are sex chromosomes. The autosomes are designated as pairs 1-22.In a normal female, karyotype is reported as - 46 XX, the sex chromosomes are XX. In a normal male karyotype is - 46 XY, the sex chromosomes are XY. The International Standard Nomenclature (ISCN) is used to report karyotype describing normal or abnormal chromosomes in autosomes or sex-chromosomes (3).

Chromosomal Analysis - The development of a reliable technique for chromosomal analysis in 1956 soon led to the discovery that several previously described conditions were due to an abnormality in the chromosome number. Within three years the causes of Down syndrome (Trisomy 21), Klinefelter syndrome (47XXX) and Turner syndrome (45X0) had been established as the abnormality due to an abnormal number of chromosomes. Other autosomal trisomies were also recognized. Gradually over the years, many other malformations or birth defect genetic syndromes were discovered in which there was loss or gain of chromosomal material. Around 20,000 chromosomal abnormalities have been registered on the basis of laboratories databases.

Chromosomal aberrations such as deletions, duplications, translocations and inversions can be demonstrated by the so called 'Karyotype Test' which reports the Human 46 chromosomes and any abnormalities in those which may affect the child, siblings or parents (2).

Thus, karyotype test detects chromosomal aberrations - both number & structural changes and hence it is a useful test in the diagnosis of genetically affected children or adults. It can be detected prenatally in a fetus by chromosomal analysis of amniotic fluid, or chorion villi during appropriate time of pregnancy. Invasive prenatal testing like amniocentesis (14-17 weeks pregnancy) and chorionic villi sampling (10-13 weeks pregnancy) are used for performing karyotyping or fluorescent in situ hybridization (FISH) tests in high-risk pregnancy which indicate some fetal abnormality on biochemical maternal screening tests or on ultrasonography examination.

The couple karyotypes, at times are required to determine inheritance of chromosomal abnormality, if any in their affected child which helps to take precautionary measures in future pregnancy or during genetic counseling (2, 4).

Down syndrome (DS):

Down Syndrome is a most common chromosomal genetic disorder with intellectual disability, involving chromosome no. 21. This condition derives its name from Dr Langdon Down, who first described facial characteristic features in the Clinical Lecture Reports of the London Hospital in 1866 (5). The chromosomal bases of Down syndrome as extra chromosome no. 21, were not established until 1959 by Lejeune and his colleagues in Paris (4, 6).

Usually, we have two copies of each autosome, but in the Down syndrome, there are three copies of chromosome 21, called 'Trisomy 21' as shown in Fig. 2. This extra copy of chromosome causes changes during embryonic development resulting in physical and mental deficiency in a Down syndrome baby. A child born with DS has a usual life expectancy of about 40-45 years.

Most trisomic conditions are lethal in humans. The common forms of trisomic disorders observed in human beings are Patau syndrome (Trisomy 13), Edwards's syndrome (Trisomy 18) and Down Syndrome (Trisomy 21). Amongst these three, Trisomy 21 i.e. Down Syndrome (Fig.2) is most frequently observed in human species. Babies born with Patau syndrome and Edwards's syndrome are either still born or usually die within a week of their birth.

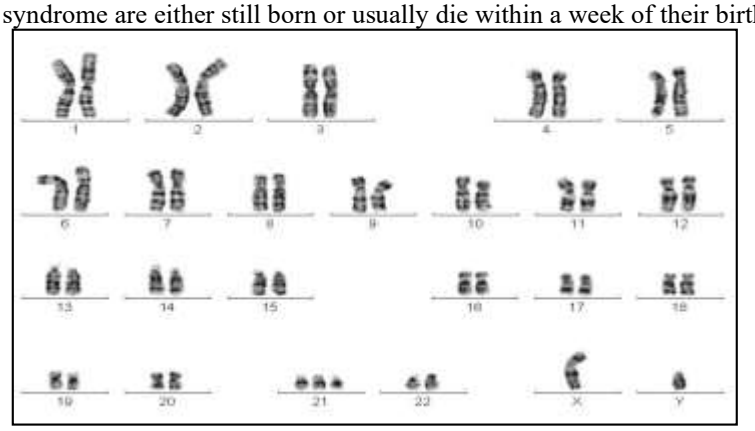

Fig 2: Karyotype of male with Down Syndrome (47, XY, +21)

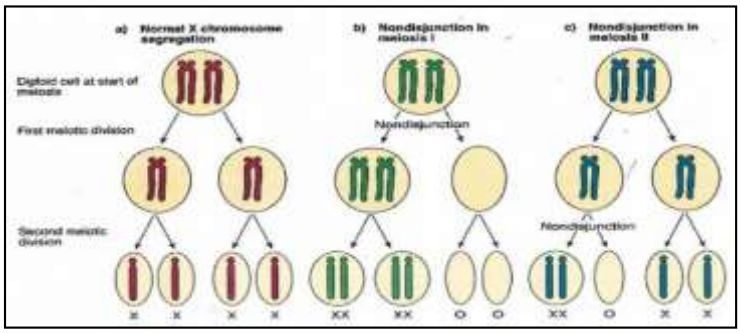

Fig. 3: Mechanism of chromosomal non-disjunction

A failure to separate the chromosomes during meiotic divisions is explained in detail as shown in Fig. 3.

- Non-disjunction in meiosis I - It is due to the failure of separation of one of the pairs of homologous chromosomes during anaphase of meiosis I as shown in Fig no.6.
- Non-disjunction during meiosis II- The gamete receives two homologous chromosomes and if subsequent fertilization occurs it leads to trisomic conception.
- Robertsonian translocation- are defined as the fusion of the long arms of two acrocentric chromosomes near their centromeric regions. Acrocentric chromosomes are chromosomes 13, 14, 15, 21, 22, and Y. It results from a breakage of two acro-centric chromosomes at or close to the centromeres of the long arms (Fig.4).
- These translocations may be balanced or unbalanced; Heterologous (two different chromosomes) or homologous (two homologous chromosomes) (7).
- The overall incidence of Robertsonian translocation in the general population is approximately 1 in 1,000, with by far the most common being fusion of the long arms of chromosomes 13 and 14 (7, 8).

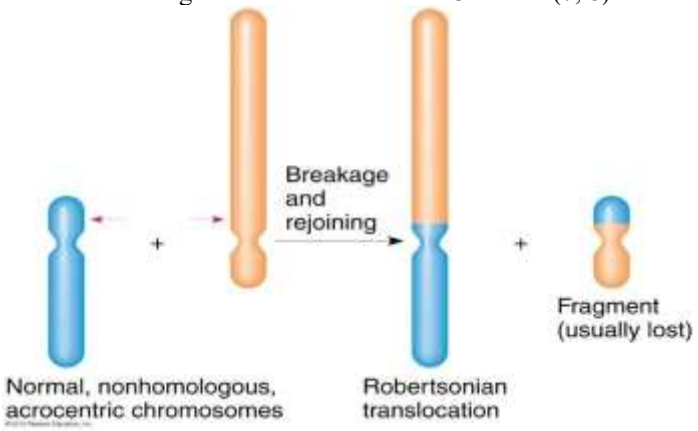

Fig. 4 showing Robertsonian chromosome translocations

Based on the types of errors, Down syndrome can show the following chromosomal abnormality in the school for ID children having Down syndrome in maximum number as below (9) -

- Trisomy 21 (88.75%) - This is the most common type of DS.
- Translocation (2.5%) - The patients have extra chromosomal material not as a separate chromosome but as a translocation of the short arm of chromosome 21 on to either a D (13, 14 or 15) or another G (21 or 22) chromosome. The patient with translocation has 46 chromosomes in all including the translocation chromosome.
- Mosaicism (8.75%) - Due to non-disjunction during an early mitotic division in the developing zygote, results in the presence of two cell lines i.e. some cells will have extra chromosome 21 and some cells will be normal or euploid cell.

Physical appearance: Down syndrome child can be easily detected because of characteristic dysmorphic facial features such as - Mongoloid face, small head, short neck, upward slanting eyes, protruding tongue, small ears, flat nose bridge, short and broad palms, Single crease in the palm (Simian crease), short/stubby fingers, poor muscle tone (hypotonia). About 15-10 % of Down syndrome babies may chow congenital heart defect, hypothyroidism or near neck spinal bone deformities. Some of these facial dysmorphism are useful diagnostic features as shown in Fig. 5.

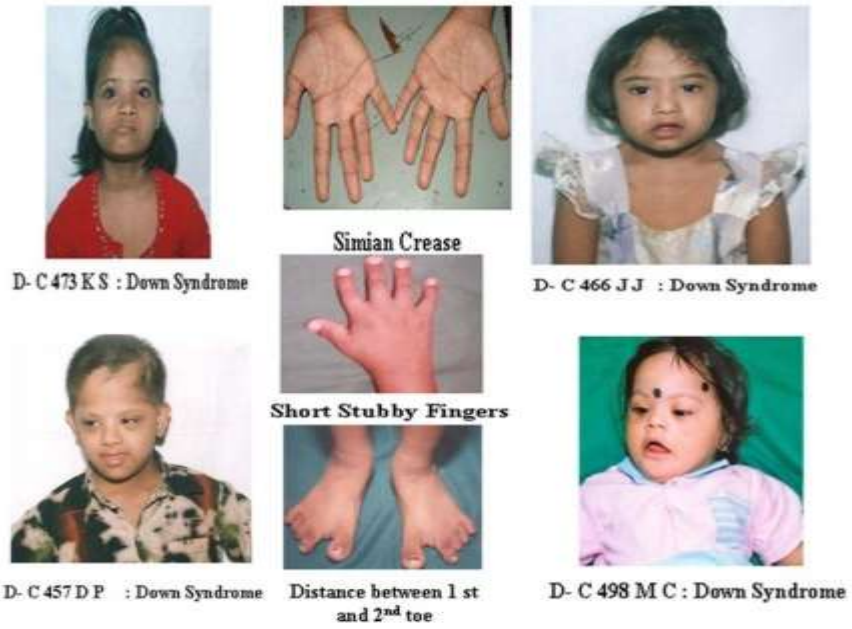

Fig. 5: showing characteristic eyes, flat nose bridge, hands, feet, face, Simian crease, etc. in infants & children.

The delayed mental & motor developmental milestones in Down syndrome are always present in terms of delayed speech and language development, delayed cognitive development, learning disabilities, memory difficulties, restlessness & or hyperactivity in the few.

The other health issues may be respiratory problems, hearing loss, vision problems, increased risk of infections, thyroid problems, digestive issues & sleeplessness. Rarely it may also be leukemia.

Risk factors responsible for birth of Down syndrome -

Advanced maternal age: - There is a well-recognized association of advanced maternal age (35 years and above) with increased risk of having a child with Down Syndrome. As age increases, the risk also increases. (9, 10). It is reported that out of the 110 DS individuals the age group of 30-39 in both maternal and paternal age group had the highest number of DS children. (10).

Previous child with Down Syndrome: -Parents with balanced translocation in DG group, then there is a 50% chance of having a child with Down's Syndrome and if translocation is in chromosome 21 there is a 100% chance of having a child with Down's Syndrome.

Family history of chromosomal abnormalities: -Couples are often referred for prenatal diagnosis because of a family history of a chromosome abnormality, most commonly DS. However, Trisomy 21 in the same family recurrence is rarely noticed, maybe because of chance error which is not repeated by nature (9).

Bad Obstetric history: - a poor Obstetric history, such as recurrent miscarriages or a previous unexplained still birth, could indicate an increased risk of problems in a future pregnancy and also relating to nutrition aspects (11, 12).

Prenatal Screening Test – Prenatal screening has become the standard of care for achieving the best possible outcomes for both the mother and the baby. Prenatal screening is intended to identify populations having an increased risk for a specific disorder for whom diagnostic testing may be warranted (13). The positive screening test for Down syndrome needs a following chromosomal confirmation test (13, 14).

The screening tests include maternal serum (biochemical) screening, carrier screening & ultrasound. These screening tests are performed with the goal of identifying women with pregnancies at high risk of chromosomal abnormalities or birth defects (15).

Prenatal screening tests during pregnancy to assess the risk of chromosomal or other genetic abnormalities are briefly described below-

Maternal Serum Screening test is performed at various stages in the pregnancy to calculate the individual risk of a fetus with a genetic disorder, especially Down syndrome in the present scenario. The specific biochemical markers show abnormal levels in case of an abnormality, e.g.

A. In first-trimester, Dual Marker screening is performed between 11- and 13-weeks' gestation by analysing serum markers - free beta-human chorionic gonadotropin (ß-hCG) and pregnancy-associated plasma protein A (PAPP-A). Maternal serum concentration of ß-hCG is higher and PAPP-A is lower in fetuses with Down syndrome (13, 15). Nuchal translucency (NT) scan value along with maternal age serum markers value is used for risk estimation of aneuploidies such as Down syndrome, Edward syndrome, Patau syndrome, and Turner syndrome (16). The detection rate for combined screen tests is >90% with a 5% false positive rate (13, 15, 17). This screening provides results at an early gestational age, allowing patients time to interpret results and make decisions regarding further pregnancy care (18).

b. Second-trimester Quadruple marker screening is generally performed between 15- and 22 weeks pregnancy and involves serum measurements of proteins including beta-hCG, alpha-fetoprotein (AFP), inhibin A, and unconjugated estriol (uE3) (16). Quadruple marker screening can screen for open neural tube defects in addition to the above-mentioned aneuploidies (18, 19). It shows 81% sensitivity with a minimal - 5% false positive rate (14).

Ultrasonography (USG) is now ubiquitous in pregnancy management; nearly all women undergo a minimum of one USG as routine care (19). The high-tech machine with better resolution can detect morphological and biometric abnormalities of the fetus warranting additional management care for that specific mother.

a.First-trimester ultrasonography (11-13+6 weeks) can be used to evaluate nuchal translucency (NT) and other soft markers like nasal bone, ductus venosus, and tricuspid regurgitation as a screen for aneuploidy and major malformations.

b.Second-trimester transabdominal ultrasonography (18-20 weeks) is recommended to screen for structural abnormalities and various malformed conditions.

Overall detection rates for USG screening are 83% for abnormalities incompatible with life, 50% for serious abnormalities with the possibility of survival, and 16% for abnormalities requiring immediate care post-birth (13). Although ultrasound can be ideal to identify defects such as open neural tube defects, combined serum screening & USG is intended to identify women with high-risk pregnancies. Numerous options for serum screening are available with varying test criteria and timing of employment (15, 16).

Non-Invasive Prenatal Screening (NIPS) or cell-free DNA testing is a next-generation sequencing (NGS) based technology that involves isolation of cell-free fragments of (fetal) DNA from the maternal serum sample (20). The demonstration of fetal cell presence maternal circulation and cell-free fetal DNA (effDNA) in maternal plasma and serum, have led to further advancements in the field of NIPS Test. (17). Results are typically reported with aneuploidy detected or no aneuploidy detected or as high- or low-risk for aneuploidy and sex chromosome abnormalities (21, 22). The positive predictive value is reported as 96% for trisomy 21, 98% for trisomy 18, and 53% for trisomy 13 (23). Moreover, the overall positive predictive value for fetal sex chromosome abnormalities was 77.3% (24). Zhou et al (2014) used non-invasive prenatal testing (NIPT) in detecting the chromosomal aneuploidies like trisomy 21,13 & 18. According to their findings, NIPT detected positive cases of aneuploidies, which were further confirmed by invasive prenatal testing like amniocentesis or chorionic villus sampling for chromosomal analysis. Hereby they concluded that with the use of non-invasive prenatal testing (NIPS), approximately 99% of invasive diagnosis can be avoided, thus reducing the testing of invasive diagnostic procedures (25).

Additionally, the above mentioned biochemical prenatal screening, along with USG is used to identify fetal abnormalities such as congenital defects, lung maturity, open neural tube defects, and risk of aneuploidies which are generally associated with DS. (11).

Prenatal Confirmatory Diagnostic Tests:

Although screening tests are a good indicative test for abnormalities, diagnostic tests need to follow screening. Diagnostic testing allows patients to know whether their pregnancy may be affected by a particular genetic condition with as much certainty as possible.

Advanced maternal age above 35 years is the most common indication for diagnostic testing in the United States. Other common indications include positive aneuploidy screening results, known family history of genetic disorders, or abnormal ultrasound (19). If the non-invasive screening test is positive, then invasive confirmatory tests are carried out.

The prenatal confirmatory diagnostic test includes two main techniques for removing the fetal tissue for chromosomal analysis which are explained below in brief-

Chorionic Villus Sampling (CVS) - Under ultrasonography guidance, at 9-11 weeks of gestation, this pre-natal diagnostic procedure is used for aspiration of chorionic villus tissue by an experienced doctor. CVS is fetal in origin, which generally forms a placenta. Chromosome analysis can be undertaken on chorionic villi either directly, looking at metaphase cells from actively dividing cells, or following culture. A 1-2% risk of causing miscarriage is predicted but in the best hands it is almost negligible. Pregnancy loss attributed to CVS is approximately 1 in 455 (26).

Amniocentesis - This technique involves the aspiration of 16-20 ml of amniotic fluid through the abdominal wall under ultrasound guidance by the experienced fetal medicine expert having PCPNDT license (27). This is usually performed in the 16-17th week of gestation. The sample is spun down to yield a pellet of cells which is resuspended in Amniomax media to grow and after 7-14 days, cells are ready for chromosomal analysis, metaphase staining and further observation under the microscope. The steps involved to observe chromosomes in the metaphases are shown in Fig.6.

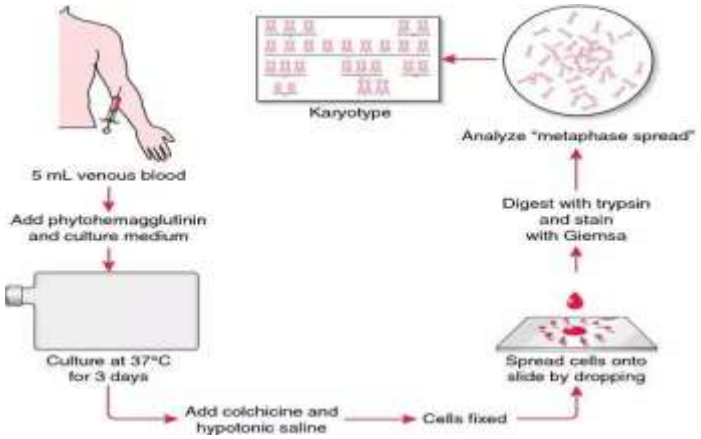

Fig. 6: Sample Preparation for chromosomal analysis

(Source- Mueller & Young, 2001)

The 0.5-1% of fetal risk is associated and that if the result is abnormal there will be possibility of considering a late mid trimester termination of pregnancy (6). The frequency of both CVS and amniocentesis has decreased with the recent increased uptake of cell-free DNA (NIPS) screening (26).

Prenatal Diagnosis in Down Syndrome:

The pregnant woman showing high-risk of a Down syndrome baby on biochemical, USG and/or NIPS testing as described above, she needs to undergo prenatal chromosomal test using either CVS or amniotic fluid depending on the gestation weeks. Once it is ruled out, the pregnancy is continued under further doctor's care. However, if the diagnostic chromosomal test confirms Down syndrome, e.g. as shown in Fig.2, genetic counseling is essential with the couple to explain the nature & inheritance of this genetic syndrome with ID, and further reproductive options of termination or not (28).

Genetic counseling (GC) is a process of communication and education which addresses the concern relating to the nature of genetic condition, prognosis, genetic tests available, development and /or transmission of a hereditary disorder. The GC is an integral part of pre-& post- prenatal diagnostic testing.

PCPNDT : Pre-Conception and Pre-Natal Diagnostic Techniques Act

Objective:

In view of the above background, the present case study was undertaken on three high-risk pregnancy cases for Down syndrome referred to the Genetic Centre and analysed from the student's perspective (the first student author) who undertook internship at the same Genetic Centre. The objective was to demonstrate the impact of proper genetic testing & counseling during pregnancy to reduce recurrence risk in a family and the incidence of ID & Down syndrome in general population.

MATERIALS AND METHODS

Study Design: The research focuses on analysing existing prenatal data to identify recent incidence & abnormalities associated with Down Syndrome in high-risk cases referred to the prenatal laboratory (MILS Labassure International, Mumbai).

Data Source: The primary dataset consists of anonymized Genetic counselling & prenatal test reports provided by the laboratory at which training for prenatal testing was taken by the student (1st Author). These reports include profiles from Individuals who are having high risk for DS.

All data were de-identified prior to access to ensure patient confidentiality and ethical compliance.

Study Population: The study was conducted on 3 antenatal cases who were referred for high risk screening with clinical suspicion of DS & or other abnormalities based on prenatal screening test results and advanced maternal age.

The detailed family history & prenatal screening tests, their results and post-test genetic counseling done in case of each case is noted.

Methodology: The standard procedure for karyotyping as per the method of Mueller & Young, (2001) (29) includes steps like sample collection, cell culture, harvesting, slide preparation, Giemsa staining, microscopic analysis. Peripheral blood is the most common sample. 2-3 ml of venous blood is collected in a heparinized green tube under sterile conditions (Fig. 6). In prenatal diagnosis, amniotic fluid or chorionic villus samples are used.

The cells are cultured in a special media containing phytohemagglutinin (PHA) for 72 hours at 37°C which stimulates cell division and increases the number of metaphase cells. Colchicine is added to arrest cells in metaphase. The cells are then treated with hypotonic solution and fixed with methanol-acetic acid to spread the chromosomes. This cell suspension is dropped onto clean glass slides and air-dried. Giemsa staining, commonly known as G-banding, is performed to produce characteristic dark and light bands on each chromosome for identification.

Under a microscope, at least 20 metaphase spreads are analyzed. The chromosomes are arranged, paired, and counted to make a karyogram. In Down syndrome, an extra chromosome 21 is observed, resulting in a female 47, XY+21 or male 47, XX+21 karyotype. The final report includes the total chromosome number, sex chromosomes, and any numerical or structural abnormalities in the pattern as per the ISCN (as shown in Fig. 2). Genetic counseling is recommended following the report.

RESULTS

All 3 high-risk pregnancy cases were advised to do prenatal chromosomal testing.

The details about age, high-risk genetic factors such as advanced maternal age, prenatal screening tests and their results as well as prenatal chromosomal test samples & final results are given in Table-1. The comparative analysis of the screening & confirmatory diagnostic tests was conducted in order to determine the significance of the genetic steps taken (Table 1).

None of the couples had undergone pre-conception carrier screening test for detecting chromosomal translocation

Table 1: Comparative Summary of Three High Risk Prenatal Cases

Parameters	**Case 1 (MILS-GEN-48)**	**Case 2 (MILS-GEN-64)**	**Case 3 (MILS-GEN-65)**
Age	36 Years	26 Years	31 Years
Family History	H/o RPL (Three 1st Trimester miscarriages)	Uncle's Son is DS child	NA
Genetic Screening & Diagnostic Tests			
A. Maternal Biochemical Risk (Yes/No)	Yes (Quadruple marker shows T:21risk - 1:93)	Yes (Dual Marker shows T:21 risk - 1:113)	Yes (Dual Marker shows T:21risk - 1:9)
B. USG Findings (Normal/Abnormal)	Normal	Normal	**Abnormal**- Nasal Bone Absent NT- 4.0mm
Carrier Screening - Couple Karyotype	Not done	Not done	Not done
NIPS (Done/Not Done)	Not Done	Done, High Risk for Trisomy 21	Not Done
Confirmatory Test (Yes/No)	Yes, Karyotype +FISH from amniotic fluid	Yes, Karyotype +FISH from amniotic fluid	Yes, Karyotype +FISH from amniotic fluid
Results	Normal	Normal	**Abnormal - Trisomy 21**
Genetic Counseling & Reproductive Options Given	GC done & it is advised to continue the pregnancy	GC done & it is advised to continue the pregnancy	Opted for termination of pregnancy after proper post-test GC.

Case 1 [MILS-GEN-48]:

A 36-year-old woman with a history of three recurrent pregnancy losses (RPL) in first- trimester was referred with advanced maternal age of 36 years. Her quadruple marker screening test reports showed high risk for Down syndrome (Trisomy 21) as 1:93. Her Nuchal Translucency Scan (NT USG) was within normal limits and nasal bone was also present. Non-invasive prenatal screening was not done due to cost constraints and the patient directly opted for confirmatory prenatal amniocentesis test which revealed normal fetal karyotype and FISH test results (Table 1) and ruled out any chromosomal abnormalities. Post-test Genetic counseling was done to ensure the baby's health and the pregnancy was continued.

Case 2 [MILS-GEN-64]:

A 26-year-old woman with a family history of Down syndrome in her nephew, was referred with the dual marker biochemical screening & USG test reports. It showed high risk for Trisomy 21(1:113) with normal USG findings. Non-invasive prenatal screening (NIPS) was also done which revealed the high risk for Trisomy 21. Hence, the amniocentesis was advised which revealed normal karyotype findings and FISH test. The appropriate genetic counselling assuring the mother of exclusion of Down syndrome which was suspected due to the screening test results. The couple took a decision to continue the pregnancy.

Case 3 [Mils-Gen-65]:

A 31-year-old pregnant lady was referred for prenatal diagnostic testing with high risk on dual marker biochemical screening for Trisomy 21 (1:9), with abnormal USG findings including absence of nasal bone and increased NT-4.0mm (normal NT 0.5 to
2.5 mm) in Nuchal Translucency Scan. The NIPS test was not done. Amniocentesis with karyotype offered due to high-risk on both maternal screening & abnormal USG findings. The confirmatory chromosomal diagnostic test showed positive result for Trisomy 21 (Fig. 2). Post-test genetic counselling was done explaining nature of genetic syndrome, its inheritance, future consequences related to the positive report to the patient & her partner. Understanding the future ID in the baby & considering the social & economic consequences of Down syndrome child, the young couple took the decision of termination of the pregnancy as per PCPNDT guidelines.

DISCUSSION

In India, it is estimated that approximately 30,000-35,000 babies are born with DS every year annually and prevalence rate may be between 1 in 800-1,000 live births (30). In the cytogenetic study of 555 ID individuals from the Institute, Down syndrome was reported to be the most common chromosomal disorder, representing 45% of cases (31). Of the 250 individuals with Down syndrome, 57.6% were male and 42.4% were female, indicating almost absence of sex preference. Similarly, not only the advanced maternal age, but younger women between age group of 18-22 years can have Down syndrome has been demonstrated in the Indian study (9) which may be due to early marriages as a custom in India.

In order to understand the awareness about Down syndrome & its prenatal screening, the study was conducted in a tertiary hospital in India. Out of 267 pregnant women, only 156 (58.4%) had heard about Down syndrome and 85 % women agreed that DS babies had mental impairment. But only 21.1% had knowledge about Down syndrome and 11% had good knowledge about screening tests (32).

Down syndrome is a congenital birth defect as a result of a genetic aberration and not a disease which many people are not aware of. The incidence of Down syndrome is rising nowadays with late pregnancies due to late marriages and career preferences. The risk increases with maternal age above 35 years (33). When a baby with Down syndrome is born, there is a significant morbidity on the affected individual and the family both, financially and emotionally (30). Due to the advancement in medical sciences, the life expectancy of an individual with Down syndrome has increased, it becomes important for a pregnant woman to know about options available for prenatal testing and decide suitable management options.

In many developed countries, ‘universal prenatal screening’ for common chromosomal aneuploidies has become part of routine antenatal care. Countries such as the United States, United Kingdom, Canada, and most of Western Europe offer first- trimester combined screening or Non-Invasive Prenatal Testing (NIPT) to all pregnant women, regardless of maternal age (15,16). The rationale is that age-based screening alone misses a large proportion of cases, since approximately 80% of babies with Down syndrome are born to women under 35 years due to higher birth rates in this age group (9, 33). By screening every pregnancy, healthcare systems aim to provide early and accurate risk assessment, allowing for timely diagnostic testing and informed reproductive decision-making.

A well trained ‘Genetic Counselor’ (34), dealing with Down Syndrome, with his/her ability to communicate explains the couple/family mode of inheritance, genetic recurrence risk and choices or options available for dealing with Down Syndrome risk. The communication skills during prenatal ‘Genetic Counseling’ with long term contact support is the success of genetic counseling when various appropriate tests of genetic screening & diagnosis for prevention of recurrence are explained with their implications (35). Of course, this process includes complex psychological and emotional situations that can influence the counseling dialogue. It is estimated that currently, there is a dire need of genetic counselors in India, considering about 27 million annual birth rate and about 30,000-35,000 Down syndrome births.

The impact of universal screening programs has been significant in reducing late diagnoses and improving preparedness. In the UK, the NHS Fetal Anomaly Screening Programme reports detection rates of >90% for Trisomy 21 with combined screening (36). Similarly, in the US, the widespread adoption of NIPT since 2011 has increased detection to >99% while reducing the number of invasive procedures (21). However, these programs are coupled with mandatory genetic counseling to ensure that results are understood in a non-directive manner and to provide support for families regardless of their choices (15). This model of "screen + counsel + support" is considered a key strategy for reducing both the medical and psychosocial impact of aneuploidies on families and national health systems.

The importance of genetic counselling in Down Syndrome and discussing different ways in order to treat and take care of the individual having Down Syndrome and discussing the management, clinical manifestation, complications associated with Down Syndrome, cannot be overlooked. On the basis of prenatal diagnosis and GC, the couple can either carry on the pregnancy or parents can plan and prepare themselves for a baby with Down Syndrome or terminate it, the latter considering the socio- economic & psychological consequences.

Knowledge about both Down syndrome and screening tests available to general population is still poor & mostly confined to urban cities. If adequate information can be provided to the pregnant women and her partner regarding Down syndrome & genetic screening tests at their earliest antenatal visit, they can take an informed decision. Such essential education equips pregnant women and their families with the knowledge needed to make informed decisions about Down syndrome screening.

CONCLUSION

The significant role of prenatal diagnosis to reduce the impact of Down syndrome in Indian population is thus emphasized by the present study through three case scenarios with high risk for Down syndrome babies. The NIPS & USG screening

is more reliable & accurate. It is evident that every woman irrespective of their age group should undertake screening tests as it not only gives the possible information about the baby's health during pregnancy but also informs whether the fetus is at high or low risk of having Down syndrome. Genetic screening tests provide the parents with an option of undertaking more diagnostic procedures to confirm if the unborn child has any chromosomal abnormalities like Down syndrome. This ability to detect a birth defect, chromosomal abnormality or congenital malformations in utero, has paved way to increased awareness amongst the people to undertake screening tests, at least in big urban cities.

The non-invasive screening tests currently available to predict the risk of Down syndrome along with other anomalies can be incorporated along with basic genetic counseling in regular rural & district prenatal clinics making these services as an integral part of health system. The study also emphasizes the need of advanced prenatal NIPS screening & proper genetic counseling to reduce the incidence of birth defects, thereby reducing the social, mental, & economic impact on the family & nation at large.

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