Discussion

6.1 Introduction

In this study chromosomal abnormality observed in 85 cases and that is 7.29%, from total number of 1165 cases enrolled. The world wide abortion risk for amniocentesis procedure is 0.5 to 1%. If we compare the abortion risk with the abnormalities observed, the high percentage of chromosomal abnormalities itself suggest the importance of amniocentesis in prenatal diagnosis (Figure- 6.1). Both types of abnormalities, numerical and structural are observed in this study. In numerical abnormalities trisomy 21 is the most frequent and highest anomaly (Karaoguz, 2006) observed followed by trisomy 18, monosomy and trisomy of sex chromosomes. In structural abnormalities inversion of autosomal chromosome is the highest abnormality observed followed by translocation, inversion of one of the sex chromosomes, derivatives, deletion and duplication.

Abnormalities observed are much higher than that of world wide abortion risk

![Importance of Prenatal Diagnosis](image)

(Abnormalities observed in amniocentesis and abortion risk)

(Figure- 6.1)

About 50% of women are ready to take the risk of amniocentesis despite of having abnormal child. The single most important factor which effects the decision is the type of soft marker and association of that marker with abnormality.
Cytogenetic diagnosis gives the precise chromosomal status of an individual and incidence of chromosomal abnormalities (Table- 6.1). The diagnosis made is permanent and not likely to alter by medicines or environmental factors (Except in some malignancies ad hematological syndrome) with no much scope to alter the situation. The decision of management and reproductive options are entirely based on these results.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency (per 1000 births)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All abnormalities</td>
<td>9.1</td>
</tr>
<tr>
<td>Autosomal trisomies</td>
<td>1.4</td>
</tr>
<tr>
<td>Balanced autosomal abnormalities</td>
<td>5.2</td>
</tr>
<tr>
<td>Unbalance autosomal abnormalities</td>
<td>0.6</td>
</tr>
<tr>
<td>Sex chromosome abnormalities</td>
<td>-</td>
</tr>
<tr>
<td>In phenotypic males</td>
<td>1.2</td>
</tr>
<tr>
<td>In phenotypic females</td>
<td>0.75</td>
</tr>
</tbody>
</table>

(Chromosomal abnormalities in unselected newborns)

(Table- 6.1)

(Gogate, 2006)

6.2 **Correlation of chromosomal patterns with high risk factors**

6.2.1 **Advanced Maternal Age**
In this high risk factor study revealed the incidence of chromosome abnormalities at amniocentesis by maternal age. The frequencies of Down syndrome (Trisomy 21) and other chromosomal abnormalities are well known to increase with maternal age (Lee, 1995). In this study of 1165 cases, the incidence of chromosomal abnormalities in women aged 35 and other older increased with maternal age. In 1165 cases 525 cases were of maternal age as a high risk factor. Out of 525 cases 38(7.25%) cases were observed abnormal. In 38 abnormal cases the most common and highest chromosomal abnormality observed is of 18(47.37%) cases of trisomy 21.

The correlation of maternal age with chromosomal abnormalities suggests that incidence of Down’s syndrome increases with maternal age. Study also suggests that not only trisomy 21 but incidence of other chromosomal abnormalities also increase with maternal age. The occurrence of meiotic non-disjunction is largely influenced by maternal age. During fetal development female amass their lifetime supply of oocytes, a significant proportion of which regress, over time. Aging process of the oocytes and environmental influences adversely affect the meiotic spindle (Carothers, 1999). Several hypotheses are devotees to the damage of spindle components whether by intrinsic factors or by the accumulation of environmental insults over the long meiotic process (Figure-6.2). There are many agents such as irradiation and heavy metal ions that could affect oocytes (Gardner, 2004).
Meiosis in an younger female oocytes

Meiosis in an older female oocytes

(Figure- 6.2) (Gardener- 2004)
The following graphing presentation shows that incidence of trisomy21 (Graph 1) and other chromosomal abnormalities (Figure-6.2) increases with maternal age.

**Figure – 6.3**

**Incidence of Trisomy-21 and advanced maternal age**
The data analysis and graphical presentation clearly concludes that the incidence of trisomy 21, lethal autosomal abnormality and other chromosomal abnormalities increases with the advanced maternal age (Figure- 6.4). This is also shown in the study done by Hassold et al. 1996.

6.2.2 Positive Maternal Serum Screening (MSS)
Maternal serum screening in 1st and 2nd trimester is a known voluntary accepted method for screening of chromosome 21, 18 and NTD in the general population (Nicolaides, 2003). In screen positive cases, confirmation of the chromosomal anomaly requires invasive procedure like amniocentesis. Majority cases show normal fetal chromosomal pattern. Amongst the abnormal karyotypes, trisomy 21 and trisomy 18 are expected but unusual chromosomal abnormalities also come as surprises (Myra, 2005). In the present study data revealed that the incidence of
unexpected result is higher than that of expected results. The unexpected results mostly the structural chromosomal rearrangement may affect the quality of life of the fetus. The fetuses born with the structural abnormality may have risk of mentally and physically abnormality (Barisic, 1996). The data from study concludes that all positive maternal serum screening cases should be offered complete karyotype and counseled for the expected and unexpected results.

**Expected and unexpected chromosomal patterns and Maternal serum Screening**

In this study, total 366 cases were referred with positive maternal serum screening. Out of 366 cases 332 (90.71%) observed with normal karyotype while 34 (9.28%) confirmed with chromosomal abnormalities. As mention earlier that maternal serum is the test which is to screen expected results like trisomy 21, trisomy 18 and NTD. In this study it is observed that the percentage of unexpected results is higher (58.82%) than the expected results (41.17%) (Figure-6.4). The unexpected result plays an important role in the quality life of fetus after birth.

Invasive procedures like amniocentesis are expensive, in this part; maternal serum screening plays an important role to screen the high risk population. Trisomy 21, 18 and NTD are screened in maternal serum screening. In many studies it is concluded that Down syndrome is the most common genetic abnormality (Kuller, 1996). The abnormalities apart from these are also detected and come as surprise in invasive procedure. Numerical unexpected abnormalities like Klinefelter and turner syndrome where the reproductive life and other problem associated are also important.

Structural abnormality also manifest as a clinical syndrome due to losses or gain of chromosomal material resulting in deletion or duplication. The fetus with reciprocal translocation is simple two ways translocation occurs between two chromosomes, usually in autosomes. Other translocations are more complex ones or ones where sex chromosomes are involved. Fetus carrying this type of translocation may have the mental or physiological abnormality. Very unbalanced conception will abort even before prenatal diagnosis. If the fetus carries a de novo translocation, studies demonstrate that the risk for birth defects or mental retardation or both is in the range of 6-10%.
Some uncommon abnormalities like micro deletion may be surprise but are not detected by cytogenetic, FISH is preferred. Other structural abnormalities like inversion, insertion, duplication etc. have to be evaluated with reference to point of breakage and whether known genes have been disrupted. A risk of 9.4% is quoted by counselors (Linden, 2002) for De novo inversion resulting in phenotypic anomalies, but most of the time reviews of literature are the most useful guideline for decision making.

The graphical presentation shows that incidence of unexpected results are higher than that of expected outcomes in positive maternal serum screening.

6.2.3 Abnormal Ultrasound with and without NT
USG plays an important role in genetic disorder. Most fetuses with structural malformation have normal outcomes. USG has a part of routine antenatal management. A single soft marker may
also be associated with variable risk of anuploidy depending on the marker and mother age. If the USG is combining with the other factor like maternal age, maternal serum screening the detection rate increases (Shrada, 2007). The obstetric history plays an important role in the decision regarding invasive procedure.

This study reviewed the important fetal ultrasound markers. Total 162 cases are enrolled with the abnormal USG. Out of 162 cases 148(91.36%) cases had normal karyotype and 14(8.64%) cases observed with chromosomal abnormalities. The distributions of chromosomal abnormalities in this category are as follows, 6(42.86%) cases with trisomy 21, one (7.14%) case of triploidy, 6(42.86%) cases with inv 9 and one (7.14%) case of inv-1.

The fetal nasal bone is visualized by sonography throughout the pregnancy. In 1866 down noted that the common abnormality of trisomy 21 is small nose (Farkas, 2001). A study of 105 patient shows that 49.5% patient have short nose. Recent reports have shows that absence fetal nasal bone or nasal hypoplasia is an important marker for anuploidy both in the first and second trimester. Most of the study shows that absence of the nasal bone is associated with trisomy 21 at 11 to 14 weeks of gestation. The combine data from various study shows that fetal nasal bone was absent in 1.4% of chromosomally normal fetus and 69% of fetus with trisomy 21. In second trimester more number of trisomy detected based on nasal hypoplasia (Tamsel, 2007). Several other studies have demonstrated a strong association between an absent nasal bone and trisomy 21, and other chromosomal abnormalities (Nyhan, 1988).

The other abnormal soft markers and the chromosomal abnormalities, associated with them, are listed bellow. In this study USG abnormalities associated in most of the caeses with nasal bone was trisomy 21, which is the highest and observed in 5 cases. Short humerus and femur are also associated with trisomy 21. The other USG marker in which the numerical and structural chromosomal abnormalities associated are echogenic bowel, echogenic cardiac focus, skeleton dysplasia, echogenic foci, CHD, duodenal atresia and clef lip palate.
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Skeleton</th>
<th>Abdominal</th>
<th>Nasal Bone</th>
<th>Cardiac</th>
<th>Growth</th>
<th>Abnormalities observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Hypoplastic Nasal Bone</td>
<td></td>
<td></td>
<td></td>
<td>47, ** +21</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>Echogenic Cardiac Focus</td>
<td></td>
<td></td>
<td>46, ** inv(9)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Echogenic Bowel</td>
<td></td>
<td></td>
<td></td>
<td>69, ***</td>
</tr>
<tr>
<td>4</td>
<td>Skeletal Dysplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46, ** inv(9)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Echogenic Bowel</td>
<td>Absent Nasal bone</td>
<td></td>
<td></td>
<td>47, ** +21</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Echogenic foci in lt. Ventricle</td>
<td></td>
<td></td>
<td></td>
<td>46, ** inv(1)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>IUGR + Oligo</td>
<td></td>
<td></td>
<td>46, ** inv(9)</td>
</tr>
<tr>
<td>8</td>
<td>fetal long bone</td>
<td>abdominal circumference disproportionate</td>
<td></td>
<td></td>
<td></td>
<td>46, inv(9)*2</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>Absent nasal bone</td>
<td></td>
<td></td>
<td>47, ** +21</td>
</tr>
<tr>
<td>10</td>
<td>Short Humerus &amp; Femur</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>47, ** +21</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>Intra cardiac Echogenic foci</td>
<td></td>
<td></td>
<td>46, ** inv(9)</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>overdistended stomach, Dilated duo denum</td>
<td></td>
<td>?duodenal atresia</td>
<td></td>
<td>47, ** +21</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>no ossification of nasal bone</td>
<td></td>
<td></td>
<td></td>
<td>47, ** +21</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>Cleft lip palate</td>
<td></td>
<td></td>
<td></td>
<td>46, ** inv(9)</td>
</tr>
</tbody>
</table>

**Ultrasound markers and chromosomal pattern observed**

*(Table- 6.2)*

6.2.4 **Increased Nuchal Translucency NT**

Total 29 cases enrolled in the study with increased NT. In abnormal 4 cases, 3(75%) cases were trisomy 21 and one (25%) (Figure- 6.6) case is with derivative of chromosome number 13 and 14. High incidences of trisomy 21 suggest that increased NT is associated with Down’s syndrome (Trisomy 21).

The various studies show that NT has the power full potential to detect chromosomal anuploidy. Study of 200000 pregnancies demonstrate that NT screen can identifies about 75% of fetuses with trisomy 21 and other chromosomal abnormality. With the association of some chemical
marker like PAPP-A and Beta hCG with ultrasound, it is possible to identify 90% of the chromosomal aneuploidy (Shrada, 2007).

(Nuchal Translucency and chromosomal abnormalities observed)
(Figure- 6.6)

6.2.5 **BOH (Bad Obstetric History)**
In BOH cases, total 20 cases enrolled in the study. Out of 20 cases, 18(90%) were normal and 2(10%) cases observed with structural abnormalities and were both inv of chromosomes number 9.

It is well accepted that at least 50 percent of all first trimester spontaneous abortion are cytogenetically abnormal. However, chromosomal anomalies are implicated much less frequently as a cause for recurrent spontaneous abortion (RSA). The most important non-sporadic factor is when either parent is a carrier of a balanced translocation. Recurrent miscarriages might result from two different situations producing chromosomal anomalies.
Structural chromosomal anomaly is seen in about 3-5 percent of couples with a history of RSA. The most common type is the Robertsonian translocation, although inversions and ring chromosomes might also occur.

Aneuploidy is the commonest chromosomal anomaly seen in sporadic miscarriages (86% of cases), of which trisomies are the commonest. Aneuploidy generally occur de novo, due to a faulty meiosis but certain couple appear to have a risk of recurrent aneuploidy. In such cases there appears to be an increased association with chromosomal breakpoints, or chromosomal variants such as length differences and short arm polymorphism of acrocentric chromosomes. Aneuploidies are associated with increasing maternal age and this is relevant not only in sporadic miscarriage but also in RSA.

As many as 5 percent of all couple trying to conceive have two and 1 percent have three or more consecutive losses. Recurrent miscarriage is a condition that could have more than one contributory factor. Uncertainties regarding the causes and controversies surrounding the management make the condition a particularly frustrating problem for the physician as well as the patient. The spontaneous resolution rate of this condition may be high but the distress caused by the repeated pregnancy loss and with all the newly emerging data coupled with our recent abilities to document etiological factors in many cases justifies the investigation of affected couples.

6.2.6 Previous affected child

Total 136 cases referred for the risk factor in which previous child is affected and have some chromosomal abnormality. Out of 136 cases, 125(91.91 %) cases observed with normal karyotype, 11(8.09%) cases observed with chromosomal abnormalities. No numerical abnormalities observed in this high risk factor. The correlation with this factor is mention below in the table.

<table>
<thead>
<tr>
<th>Previous child with abnormalities</th>
<th>Current fetus carrying abnormalities</th>
</tr>
</thead>
</table>

...
<table>
<thead>
<tr>
<th>Observed</th>
<th>Chromosome Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dandy Walkar Malformation</td>
<td>46**.t(2;6)t(10;13)</td>
</tr>
<tr>
<td>Cong Heart Disease</td>
<td>46,.inv(*)</td>
</tr>
<tr>
<td>TRI21</td>
<td>46,**.inv(5)</td>
</tr>
<tr>
<td>Omphalocele + Anencephaly</td>
<td>46,**.inv(1)</td>
</tr>
<tr>
<td>46, XX, del(18)(q21;q21)</td>
<td>46, **, del(18)(q21.2;q21.2)</td>
</tr>
<tr>
<td>Missed abortion</td>
<td>46, **, inv(9)</td>
</tr>
<tr>
<td>Hyperactivity syndrome</td>
<td>46,**.inv(9)</td>
</tr>
<tr>
<td>inv(9) on PND</td>
<td>46,**.inv(9)</td>
</tr>
<tr>
<td>Dysplastic Kidney, multicystic in 2 pregnancy, severe oligohydraminos</td>
<td>46,**, der(10), t(1;10)9q32;p13)</td>
</tr>
<tr>
<td>FKSCS, hydrocephalic died after 4 days</td>
<td>46, **inv(5)(p15.3q13)</td>
</tr>
<tr>
<td>2 UFD</td>
<td>46, **, inv(9)(p11q12)</td>
</tr>
</tbody>
</table>

**Previous affected child and chromosomal abnormalities observed in current pregnancy**

(Table- 6.3)

The recurrence risk depends on the type of rearrangement and chromosome involvement. Chromosomal abnormality in the fetus aborted is often seen in the form of triploidy or polyploidy which occurs due to post zygotic error.

There are no numerical abnormalities observed this high risk group. The structural abnormalities observed are Translocation, inversion, derivatives and deletion. Structurally rearrangement chromosomes usually manifest as a clinical syndrome due to the loss or gain of chromosomal material resulting in deletion or duplication. A loss or gain of >2% HAL cannot be tolerate by the human body and resulting in the miscarriage of the fetus.

6.2.7 Carrier parents
In carrier parents as a high risk factor, total 14 cases enrolled. The chromosomal pattern observed in this high risk factor is divided in tree category,

1. **Fetus karyo same as abnormal karyo of parents**: Total 7 cases observed. The abnormalities observed were inversion, translocation and derivatives.

2. **Fetus karyo differ from abnormal karyo of parents**: Total 3 cases observed. The abnormalities were derivatives, deletion and translocation.

3. **Fetus karyo normal from abnormal karyo of parents**: Total 3 cases were observed. In this type parents carries the translocation and inversion type of chromosomal pattern but fetuses were normal in karyotype.

**Genetic impact of three categories on the fetuses**

1. **Karyotype of the fetus is similar to that of the carrier parents**: There is no increase risk for phenotypic abnormalities in the fetus and mostly occurs as balanced translocation

2. **Karyotype of the fetus differ (De-novo) from that of carrier parents**: If the fetus carries the de-novo chromosomal patterns then the risk for birth defect or mental retardation or both increase depend on the rearrange chromosomal pattern. i.e De-novo translocation or gain or loss chromosomal segments.

3. **Karyotype of the fetus is normal to that of carrier parent**: Normal fetus with no chromosomal abnormalities.

Fetal chromosomal anomalies are known to occur due to maternal or paternal non dysfunctional or post zygotic errors. The frequency of such errors occurs due to the different procedure of meiosis in male and females. Male carriers have a very small chance of children having unbalanced forms. Female carriers of balanced translocation have a higher chance of having a child with an unbalanced chromosomal pattern (Rao, 1996). In reciprocal translocation the risk for maternal or paternal translocation is same.

Individual carry rings a chromosomal rearrangement do not have any phenotypic changes. They have normal chromosomal material, which is only rearranged. When transmitted to progeny the affect depends on the size of loss or gain of the chromosomal material and more are the chances of fetal anomaly.
The consequences are: (Hassold, 1996)

1. A normal chromosome complements leading to normal offspring.
2. Balanced chromosomes complement i.e. a translocation chromosome as in the carrier parent.
3. An unbalanced chromosome complement with a normal chromosome and a missing chromosome. This will result in monosomy for a specified chromosome.
4. Unbalanced chromosomes complement possessing both the translocation chromosome and a normal chromosome. This will result in the fertilized embryo having trisomy for a specified chromosome.

The last two combinations will result in monosomies and trisomies.

6.4 Constitutional chromosomal aberration observed

6.4.1 Autosomal trisomies

<table>
<thead>
<tr>
<th>Type of abnormalities</th>
<th>Total number of cases</th>
<th>Number of cases with chromosomal aberration observed in the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>34</td>
<td>47,<strong>,+21 (32), 47,</strong>, 9qh+, +21 (1), 47,**,t(4;6)(q31.3;q25)+21 (1)</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>4</td>
<td>47,**,+18 (4)</td>
</tr>
</tbody>
</table>

Observed trisomy in study, Trisomy 21 and Trisomy18 (Table-6.4)

Down’s syndrome (Trisomy 21): This is the commonest and best known chromosomal abnormality leading to live birth. The extra chromosome number in this syndrome is 21. The overall incidence of trisomy 21 is about 1 per 800 live births, the ratio of males to female being (3:2). The incidence of trisomy 21 is seen to increase with maternal age. The extra chromosome 21 is a result of meiotic non- disjunction, which usually occurs in maternal meiosis, usually in meiosis I. It may also result from paternal meiotic error (Song, 1997).
Though its association with maternal age is proved, Majority of the Downs’s syndrome cases are in the younger mother also. Significance of paternal age is not yet proved. In a Down’s syndrome multiple system are involved and care at a specialty centre is required. In a couple having Down’s syndrome to estimate the recurrence risk, cytogenetic pattern of the affected child and if required of the parents (Definitely if the child is not alive is necessary). (Figure- 6.7)

Approximately 96% of the Down’s syndrome patients have free trisomy TRI-21 (Figure-6.8). In 4% of the cases it occurs as translocation of the extra chromosome 21 on chromosome number 14 or a second chromosome 21, which is not observed in this study, t(14;21), t(21;21) (Gardner, 2004).
The life expectancy of Down’s affected children used to be low due to respiratory infection which were life threatening. With greater and better medical care, up to 8% of people with Down’s syndrome can live up to the age of 40 or more. The intelligence quotient is usually 25 to 70; with appropriate training Down’s syndrome children can become self-reliant. Longer life can bring problem of old age. Patients age prematurely, and may develop psychotic disorders later in life and symptoms of Alzheimer disease may be seen in middle age (Purandarey, 2009). The susceptibility to respiratory disorders decreases after childhood. The other systems that may be involved in Down’s syndrome are cardiac and digestive system.
The common phenotypical feature of Down’s baby are Flat facial profile, Epicanthic fold, Upward slanting eyes, flat nasal bridge, protruding tongue, Simian crease, gap between 1st and 2nd toes ect. (Figure- 6.9). Congenital heart disease may be seen in about one third of live births and in a higher proportion of abortuses with this syndrome. The digestive disorders are duodenal atresia and tracheoesophageal fistula, while the cardiac disorders are ASD, VSD or Fallot’s tetralogy (Ghosh, 1963). Acute lymphocytic and non-lymphocytic leukemia are other complication occurring in 10% Down’s syndrome babies. These patients are less likely to respond to treatment. Females with trisomy 21 are fertile and may have children who are normal or with trisomy 21. Males with trisomy 21 may be fertile, but have poor libido.

Other Karyotype patterns in Down’s syndrome
**Translocation Down’s syndrome**

96 percent of all patients with Down’s syndrome have an extra chromosome 21 in Group G. In the remaining 4% the extra 21 is translocated to chromosome 14 or 21.

![Diagram of chromosome translocation](http://ds-health.com/bene.htm)

The translocation chromosome replaces one of the normal acrocentrics. The karyotype of the patient is hence 46,XX/XY,-14,+t(14q;21q). The patient is therefore trisomic for 21q (Figure 6.10).

In this type the translocated chromosome comes through either of the parents who have 45 chromosomes in which one 14 and one 21 are missing, these being replaced by the translocation chromosome, t(14q;21q).

In a 21q:21q translocation Down’s syndrome the translocation is made up of long arms of two number 21 chromosomes; this may have originated as an isochromosome rather than by Robertsoian translocation. The potential progeny inevitably have either Down’s syndrome or monosomy 21, which is not viable (Thompson, 1991).

About 1 percentage of Down’s syndrome patients has mosaicism with the extra chromosome in very few cells. The phenotype may be milder in such cases.
<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>Per 1000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>1.5</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>0.12</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>0.07</td>
</tr>
<tr>
<td>XXY (Klinefelter syndrome)</td>
<td>1.5</td>
</tr>
<tr>
<td>XXX Syndrome</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Population frequency of specific chromosomal disorders
(Purandarey, 2000)
(Table-6.5)

Recurrence risk estimation in a couple with previous pregnancy of Down’s syndrome
The recurrence risk for another affected child to be born to couple with previous pregnancy of Down’s syndrome is about 1-2%. In case of child 14;21 D;G translocation the chance of another child being born with Down’s syndrome is about one in six if the mother is a carrier and about one in twenty of the father is carrier. In case of 21;21; G;G translocation type of Down’s syndrome, if either of the parents were a carrier the recurrence risk would be 100%. Prenatal screening for Down’s syndrome is possible by triple test; however this is not a diagnostic test (Chew, 1995). Prenatal diagnosis of Down’s syndrome is possible and to eliminate the risk it is recommended either in the first trimester by CVS at 9-13 weeks of gestation or in the second trimester by Amniotic fluid at 15-17 weeks of gestation (Cuckle, 2003).

Risk for offspring of second degree relatives
There is no detectable increased risk for trisomy 21 Down’s syndrome in second degree or distant relatives however, the relatives due to anxiety are keen on prenatal diagnosis and this should be offered. The risk in other two translocation types would depend as the parents karyotype pattern and if they are found to be carriers would be the same as above.

**Risk for offspring of Down’s syndrome**

With advancement in medical care, many Down’s syndrome individuals reach a fertility age group. The reports of fertility in these patients are scanty. Males with Down’s syndrome are found mostly infertile while females with Down’s syndrome are reported to be fertile and the likely risk for their offspring is 1:3.

### Clinical features of common Autosomal Trisomies.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Down Trisomy 21</th>
<th>Edward Trisomy 18</th>
<th>Patau Trisomy 13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1:1200)</td>
<td>(1:8000)</td>
<td>(1:10,000)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Pictures</strong></td>
<td><img src="image1.png" alt="Child" /></td>
<td><img src="image2.png" alt="Child" /></td>
<td><img src="image3.png" alt="Child" /></td>
</tr>
<tr>
<td><strong>In utero loss</strong></td>
<td>30%</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Life expectancy</strong></td>
<td>30-50</td>
<td>0-1</td>
<td>0-1</td>
</tr>
<tr>
<td><strong>CNS Head, Face, Neck</strong></td>
<td>MR, Hypotonia, Brachycephaly, Epicanthal folds, Hypertelorism, flat facies, excessive skin at the back of neck.</td>
<td>MR, Hypertonia, Choroids plexus cyst Micrognathia, small mouth, redundant Skin.</td>
<td>MR, seizures Microcephaly, cleft lip / palate facies, abnormal scalp defects.</td>
</tr>
<tr>
<td><strong>Hands</strong></td>
<td>Short metacarpals and phalanges, transverse palmar crease</td>
<td>Clenched hands, Clinodactyly</td>
<td>Polysyndactyly, Compactodactyly, Transverse palmar crease.</td>
</tr>
<tr>
<td><strong>Feet</strong></td>
<td>Plantar crease</td>
<td>Rocker bottom feet, Club feet</td>
<td>Polydactyly, Rocker bottom feet</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td>40% VSD, ASD, common atrium, PDA</td>
<td>40% VSD, ASD, PDA</td>
<td>80% VSD, ASD, PDA</td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td>Duodenal atresia, TOF</td>
<td>Umbilical hernia, Omphalocele</td>
<td>Inguinal/Umbilical/Hernia/Horse shoe kidney.</td>
</tr>
<tr>
<td><strong>Urogenital</strong></td>
<td>Hypogonadism, Infertility (specially in males)</td>
<td>Cryptochidism, horseshoe kidney, single umbilical artery</td>
<td>Polycystic/Ectopic kidney Bicornuate</td>
</tr>
<tr>
<td><strong>Karyotype</strong></td>
<td><img src="image4.png" alt="Karyotype" /></td>
<td><img src="image5.png" alt="Karyotype" /></td>
<td><img src="image6.png" alt="Karyotype" /></td>
</tr>
</tbody>
</table>

(Purandarey, 2009) (Gogate, 2006) and (Gardner, 2004), (Table - 6.6)

**Edward’s syndrome (Trisomy 18):** The incidence of this autosomal trisomy in live births is about 1 in 8000. Most of the fetuses with trisomy 18 are aborted spontaneously. Life expectancy is very low, postnatal survival being very rare. The female to male ratio is seen to be very high,
probably due to preferential survival. Primary meiotic non disjunction may be a cause of this type of trisomy (Parker, 2003). Maternal age is seen to be associated as in other trisomies. The effects are more severe malformation of the heart, kidney and digestive system, as skeletal defects, failure to thrive. Rocker bottom feet are a characteristic feature. Single palmer crease can be observed along with distinctive dermal pattern on all digits and hypoplastic nails. Either an entire chromosome 18 may be present additional may be seen in some cases usually with milder expression (Goldstein, 1998).

**Trisomy 18 (Edword syndrome) (Lab report)**

(Figure 6.11)

Four case of trisomy18 observed in the study and none of trisomy 13. These trisoies are rare in comparison to TRI-21. Recurrence risk for the sibling is very low. Age related risk is known. The live-birth risks are considerable less as most of such anomalies lead to spontaneous abortion.
Additionally about 1/3 of the cases are detected by amniocentesis or in termination done for abnormal ultrasound finding.

6.4.2 **Sex chromosome Trisomies and Mosaicism**

Sex chromosomal trisomies are compatible with life and symptoms vary from mild to severe hypogonadism and moderately low to normal IQ. They can be seen in mosaic form (Dewald, 1983).

6.4.3 **Sex chromosome Anueploidy**

Many of the sex chromosomal variations are compatible with life and are among the most common chromosomal abnormalities seen. Each has its own set of phenotypic expression but primarily they involve premature gonadal failure, infertility or abnormal development. The four well defined syndromes associated with sex chromosome anueploidy are:

A. **Klinefelter’s syndrome (47,XXY)**
   - The incidence of this syndrome is about 2:1000 male live births.
   - The main features are an above-average height with long thin legs; signs of hypogonadism are seen only when puberty is reached. Gynaecomastia may be seen, the penis and testis are smaller than normal. Some patients may have learning difficulties due to dyslexia. Variants of Klinefelter’s syndrome (Figure- 6.12) are seen who have more than two X-chromosome. 48,XXXY or a 49,XXXXY (Gardner, 2004).

   Chromosomal pattern may be seen. Though inactive, these additional X chromosomes are usually seen to be associated with mental retardation. The phenotype in 49,XXXXY is seen to be similar to that in Down’s syndrome. These chromosomal patterns may be
observed as mosaic with a normal male or female chromosome complement. Patient of Klinefelter’s syndrome with azoospermia or oligospermia may be benefited by fertility treatment of Intracytoplasmic sperm transfer technique they need to be told and offered prenatal diagnosis in their wives as their progeny will be at risk for chromosomal disorder (Dewald, 1983).

Karyotype of Klinefelter syndrome
(Lab Report, SRL diagnostic) (Figure- 6.12)

Clinical features of common Sex chromosome disorders.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Klinefelter’s Syndrome (XXY)</th>
<th>XYY Syndrome (#)</th>
<th>Turner’s Syndrome (* ) (45,X)</th>
<th>Triple Syndrome (XXX)</th>
</tr>
</thead>
</table>
B. **47,XXX Female**: These are the female counterparts of the Klinefelter’s syndrome seen in males. Rarely tetrasomy X or pentasomy X may be seen (Figure- 6.13). They are phenotypically normal with a taller stature. Patients may develop pubertal changes at an inappropriate age. They are fertile and bear chromosomally normal children, though the risk of a meiotic nondisjunction is increases. Patients often have history of repeated fetal wastage. This may lead to birth of children with other sex chromosomal trisomies.

(Purandarey, 2009) (Gogate, 2006) and (Gardner, 2004)

(Table- 6.7)
(Rasmussen, 2004). A significant decrease in I.Q. may be seen; this however cannot be classified as retardation. Some have learning problems. There may be an effect of late maternal age in some cases. The tetrasomy is associated with serious physical and mental retardation, while pentasomy includes severe developmental retardation and multiple physical defects similar to Down’s syndrome (Crissman, 2011).

**Karyotype of XXX syndrome**
(Figure- 6.13)

http://worms.zoology.wisc.edu/zooweb/Phelps/ZWK01047k.jpg

C. **47, XYY Male:** This chromosomal constitution is not associated with any observable phenotypic abnormalities. XYY males are very tall and often show behavioral problems such as excessively violent nature. They show normal intelligence and are not dysmorphic. The patient are fertile and have nearly no risk of having children with chromosomal abnormalities (Figure- 6.14) (Purandarey, 2009).
D. **Turner’s Syndrome:** 45,XO is the most common sex chromosomal abnormality. This is seen in a proportion of 1 in 700 female live births. However, the Turner’s syndrome can be identified at birth due to lymphedema or before puberty by distinctive phenotype or these may be lost as fetal wastage. The typical abnormalities seen in Turner’s syndrome are short stature, gonadal dysgenesis, a characteristically unusual countenance, webbing of neck and a broad chest with wide spacing of nipple, a low posterior hairline (Figure-6.15).
Many a times the condition is not diagnosed until puberty where patients are referred for primary amenorrhea or short stature (Dewald, 1983). These patients have a higher frequency of cardiovascular and renal abnormalities. Coarctatio of the aorta may be seen in some cases. The postnatal webbing of the neck may be because of the cystic Hygroma caused as a result of lymphedema in fetal life (Purandarey, 2000).
Mental retardation is not a necessary effect. Variants of Turner’s syndrome may be seen, such as those an isochromosome or a deleted form of chromosome X. These are less commonly seen than monosomy. Cases of this syndrome with a deleted Y have also been observed. Mosaic form of this syndrome along with Klinefelter’s syndrome or with 47,XXX may be seen in some cases; Ultrasound examination particularly of the genital region is suggested in 45,XO chromosomal anomaly(Figure- 6.16) (Gardner, 2004).

6.4.4 **Sex chromosomal abnormalities leading to Inter-Sex**
These cases are characterized by ambiguous internal and external genitalia. Its classification between true hermaphroditism and Pseudohermaphroditism is based on the nature of gonads. True hermaphrodites have presence of both male and female gonadal tissue, as mixed gonad or alternatively with an ovary on one side ad testicle on the other side. In Pseudohermaphroditism the gonad is either male or female. The ambiguity of the genitalia can vary from male to female. The newborns with cryptorchidism or hypospadias are labeled as males. In some patients breast development and menstruation is same. In adulthood, boys may complaints of gynecomastia or hematuria. In girls, if presents as amenorrhea and hypertrophy of the clitoris. The internal genitalia show persistent mullerian and Wolffian structure (Adam, 2012).

Cytogenetic studies in true hermaphroditism patient show 50% with 46,XX karyotypes, 20% with 46,XY karyotype, 20% with XXXY karotypes and remaining 10% with mosaic cell line with one or more additional sex chromosome in one cell line e.g. 47,XXX/46,XX or 49,XXYY/46,XX (Warburton, 1991).

**Male Pseudohermaphroditism:** These are rarely due to chromosomal aberrations. Most of the cases have 46,XX/45,X mosaic cell line. These newborns at birth are declared as male. At puberty auxiliary and pubic hair develops and deepening of voice is noted. The built is masculine but genitalia have poor masculinization. Urogenital sinus is always present. The choice of sex rearing must be determine early in life (Thompson, 1991).

Male Pseudohermaphroditism is also known to occur due to single gene mutation. The occurrence is usually familial.

**Testicular feminization syndrome- Androgen receptor insensitivity:** Earlier know as testicular feminization syndrome though is not due to any chromosomal rearrangement, it is mentioned here to complete the list. The phenotype of an individual is female but the karyotype is 46,XY or mosiaccellline of 46,XY/45,Xo leading to varying degree of intersex and occurs due to androgen insensitivity. The molecular defect is in the SRY gene. The inheritance is X- linked recessive and there is risk to normal female relative of having an XY female child. Interpretation and counseling in such case should be explained briefly (Hamamy, 2004).
Mixed Gonadal dysgenesis
This is characterized by female karyotype with ambiguous external genitalia and hypertrophied clitoris. The gonad and intra abdominal structure are asymmetric. The mulleria or Wolffian development depends on the gonads present on each side (Linden, 2002).

Female Pseudohermophrodism
In majority of cases, this occurs due to virilization of female fetus. This can be due to congenital adrenal hyperplasia or virilizing hormonal therapy in pregnancy. It is also observed in cases of masculinizing ovarian tumor in the mother (Gogate, 2006).

6.4.5 Chromosomal structural abnormalities
Structural rearrangements are a result of chromosome breakage and reunion in an abnormal site. Usually abnormalities are heritable and are a cause of chromosomal aberrations. All cells have enzymes for repair of broken strands of DNA and such repair goes on throughout the life of each cell. Some preference sites for such breaks, are known, and are called fragile sites. Chromosome breakage is frequently accompanied by exchange of material from one chromatid to another during mitosis, when the replicated chromosomes are waiting to separate into two daughter cells. This is known as sister chromatid exchange; usually no detectable effects can be seen (Pattenati, 1995).

<table>
<thead>
<tr>
<th>Type of abnormalities</th>
<th>Total number of cases</th>
<th>Number of cases with chromosomal aberrations observed in the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome Rearrangement</td>
<td>Count</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Translocations</strong></td>
<td>9</td>
<td>46,<strong>,t(2;6)(p23;q25),t(10;13)(q11.2;12.3)(1), 46,</strong>,t(5;17)(p13.1;p13)(1), 46,<strong>,t(7;8)(q11.23;p21.3)(1), 46,</strong>,t(8;15)(p10;q10)(1), 46,<strong>,t(9;21)(p13;q22)(1), 46,</strong>,t(2;16)(p23;q13)(1), 46,<strong>,t(8;13)(p21.2;q31), 46,</strong>,t(2;17)(p27;p11.2)(1), 46,**,t(4;5)(q31.3;q35)(1)</td>
</tr>
<tr>
<td><strong>Inv. Of the autosomal chromosomes</strong></td>
<td>20</td>
<td>46,<strong>,inv.(9)(p11;q12)(16), 46,</strong>,inv.(1)(p11;q12)(1), 46,<strong>,inv(5)(p11;q11.2)(1), 46,</strong>,inv(5)(p15.3;q13)(1), 46,**,inv(8)(q11.2;q13)(1),</td>
</tr>
<tr>
<td><strong>Inv. Of the one of the sex chromosome</strong></td>
<td>8</td>
<td>46,**,inv(*)(8)</td>
</tr>
<tr>
<td><strong>Deletion</strong></td>
<td>1</td>
<td>46,**,del(18)(q21.2;q21.2)(1)</td>
</tr>
<tr>
<td><strong>Duplication</strong></td>
<td>1</td>
<td>46,**,psu dup(9)(q10;q12)(1)</td>
</tr>
<tr>
<td><strong>Derivatives</strong></td>
<td>3</td>
<td>46,<strong>,der(3;14)(q10;q10)(1), 45,</strong>,der(3;14)(q11;q12)(1), 46,**,der(10)t(1;10)(p32;p13)(1)</td>
</tr>
<tr>
<td><strong>Total abnormal cases</strong></td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

**Total number of structural chromosomal aberrations observed**

*(Table- 6.8)*

**Chromosome Rearrangement**

0.5% of population is known to have a chromosomal rearrangement where the total genetic material is normal but rearranged. The types of rearrangement include translocation, pericentric and paracentric inversion and ring chromosomes (Park, 2003). Unfortunately, phenotypes may vary from normal to severely handicap. Hence prognosis in an individual case varies and careful considerations should be made while counseling the individual.

If such karyotype is observed in fetal tissue, following steps are recommended (Purandarey, 2009)
1. To confirm karyotype and check for familial origin of rearrangement (maternal or paternal origin). If similar pattern is seen, the risk to the fetus is low.

2. Literature survey for mental retardation or dysmorphology syndrome correlation for rare syndromes.

3. Confirmation with amniocentesis or fetal blood sampling using high-resolution banding or molecular cytogenetic techniques should be attempted.

The phenotype is likely to be abnormal because of deletion, duplication or in some cases both. Duplication of a part of a chromosome is comparable with partial trisomy; deletion leads to partial monosomy. Any change that leads to deviation from normal genetic complement may result in abnormal development.

**Deletion**

Deletion is a loss of chromosomal material causing an imbalance in the normal complement. The clinical manifestations depend on the size of deleted portion and the function of the genes in that segment (Figure 6.17). Deletion may occur due to chromosome breakage within one chromosome. If the pieces are reconnected to the acentric material, the resultant chromosome is short. Deletion may also be generated by abnormal segregation from a balanced translocation of inversion. This is a more likely mechanism than multiple breaks in a single chromosome. A deletion may be terminal or interstitial. High resolution banding may be used in cases of deletion that are not observed by metaphase studies. To be detectable by high resolution banding, a deletion must be at least 2000 to 3000 kb in size. FISH techniques may be used for the detection of very small deletion. Various syndromes have ascribed to certain deletions; the most well known being the Cri-du chat syndrome associated with the deletion of the short arm of chromosome 5 from band p12 to the terminal cap. Several dysmorphic syndromes are associated with cytogenetically origin in different patients may lead to differences in phenotypic expression, as can be seen by genomic imprinting that marks material and parental chromosome differently for example- Prader willi and Angelman syndrome (Thompson, 1991).
Deletion (Figure- 6.17)

Duplication
A duplication segment may be inserted in the same order as the original segment or may be reversed (Figure 6.18). Tandem duplication may arise unequal crossing over during meiosis or from a rearrangement between two chromatids during mitosis. To form a reversed duplication, the segment should be inserted upside down next to the original segment. The exact mechanism of this rearrangement is not known. Duplication is usually less harmful than a deletion. However, because duplication in gamete results in chromosomal imbalance and because of chromosome breaks that generate, it may disrupt genes. Duplication leads to some phenotypic abnormality. Certain phenotypes appear to be associated with duplication of particular chromosomal regions and functionally are trisomic for the regions (Madan, 1992).
Balanced Rearrangements
Balanced rearrangements usually do not cause any phenotypic effect, as all the genetic information is present even though at a different position. The subsequent generation are at a risk, however, as carriers are likely to produce unbalanced gametes. This may cause disruption of a gene, leading to mutation.

Inversion
Inversion involves two breaks in a single chromosome. The broken segment turns a complete 180° and reattaches to the point of breaks. Two types of inversion are known either Paracentric or pericentric (Figure 6.19). The centromere is not included in a Paracentric inversion as both breaks occur in one arm hence the arm ratio is unchanged. In a pericentric inversion the
centromere is included in the inverted portion causing the arm ratio to change. As no change is involved in the arm ratio in paracentric inversion these can be detected only by banding the preparations. Pericentric inversions are easier to identify as both the arm ratio and the banding pattern are altered (Thompson, 1991).

An inversion usually does not result in any phenotypic changes as it is type of a balanced rearrangement. A carrier type of inversion is at a risk of producing abnormal gametes that may lead to unbalanced chromosomal complements in offspring. The manifestations of the two types of inversion are different. A loop is formed when the chromosomes with an inversion, pair in meiosis I; if crossing over occurs within the loop, a deleted or duplicated chromosome can result. Inversions are only rarely implicated in chromosomal abnormalities in humans. Recombination which is a normal feature of meiosis I, is somewhat suppressed within inversion loops, but may occur in larger inversion. When the inversion is paracentric, acentric or dicentric chromosomes are formed on recombination and gametes with this unbalanced complement may not be compatible with survival of offspring. A pericentric inversion may result in unbalanced gametes with duplication or a deficiency of chromosome segments flanking the site of inversion. A particular risk is associated with pericentric inversion; the larger ones being more likely to result in viable offspring than smaller ones because the former have smaller unbalanced segments. Pericentric inversion in chromosome 9 is the most commonly seen and these are considered normal variants as there does not appear to be an increased risk of producing unbalanced gametes (Gardner, 2004).
Inversion (Figure 6.19)
Translocations

Translocation involves exchange of genetic material between two or more non homologous chromosomes (Figure 6.20). This can occur when two or more chromosomes break at the same time. Broken ends are usually sticky and the cellular enzymatic repair service usually reunites them without trouble, but mismatch may be possible. Breakage tends to occur more frequently at the fragile sites at or near the centromere or the chromosome ends and at euchromatin-heterochromatin junctions. Translocations can be reciprocal or Robertsonian.

Balanced and unbalanced Translocations (Figure 6.20)

a. **Reciprocal translocation:** This type of rearrangement occurs due to breakage of non-homologous chromosomes, either reciprocal exchange of the broken segments. Usually only two chromosomes are involved and as the exchange is reciprocal, the total chromosome number is unchanged. Very rarely three or more chromosomes may be involved. Reciprocal translocations are usually harmless as they are balanced rearrangements, but they have a risk of producing unbalanced gametes and abnormal progeny. There may be meiotic complications, particularly the risk of nondysjunction.

b. **Robertsonian translocation:** In this type of translocation two acrocentric chromosomes fuse near the centromere region with loss of the short arms. The resulting balanced karyotype has only 45 chromosomes, one of them consisting of the long arms of two copies of genes for ribosomal RNA, loss of the short arms of these
is not deleterious. Phenotypically Robertsonian translocation carriers may be normal but there is an increased risk of production of unbalanced gametes and therefore of an abnormal offspring. Of clinical importance is mainly the one involving chromosome 21 as there is a risk of producing a child with translocation Down’s syndrome.

c. A translocation of either type can render the carrier functionally sterile because of the complex synaptic structures formed. Complex translocation involving more than two breaks can cause serious problem in cell division. Small exchanges of the genetic material may produce viable dysmorphic infants, whereas large exchanges may leads to greater problem with spontaneous abortions. Sporadic translocation in chromosome 7; 14 occurs in PHA stimulated blood samples (Dewald, 1986).

d. **Insertions:** These are non–reciprocal type of translocation as a segment removed from one chromosome is inserted into a different chromosome, either in its usual orientation or in an inverted one. Insertions are, however, rare, as they require three breaks. Abnormal segregation in an inserted segment, as well as normal offspring and balanced carries.

**Marker Chromosomes**

Marker chromosomes are occasionally seen in tissue culture, mostly in the mosaic state. These are called supernumerary chromosomes as they are present in addition to the normal chromosomal complement must have a centromere. It may be derived from breakage of a chromosome with loss of the acetric fragment and non-dysjunction from its homolog at meiosis. Tiny markers often consist of little more than centric heterochromatin, whereas larger ones contain some material from one or both arms, creating an imbalance for whatever genes are present. Due to problems in identification of the marker chromosomes, its clinical significant is difficult to assess and hence poses serious problem in generic counseling. In some cases, no phenotypic effects have been seen in individuals with small markers. Some however produce severe clinical effects, e.g. a small metacentric marker identified as isochromosome 18q. Duplication of the log arm of chromosome 22 is associated with a rare dysmorphic syndrome termed. The most common findings are coloboma of the iris and anal atresia.
If a marker chromosome has an identifiable centromere, it should be included as a derivative chromosome; if no further identifications possible, and it should be denoted by the marker symbol (mar). If a marker chromosome is observed in amniotic fluid culture sample prenatal karyotype is recommended to confirm its origin as familial or denovo for genetic counseling (Purandarey, 2009).

When a marker chromosome is observed, the following point needs to be considered:

1. Is the marker de-novo or of familial origin.
2. The percentage of cells having marker chromosome in the fetus and the parents
3. Size of the chromosome compared to the ‘G’ group of chromosomes
4. Confirmation of composition by AgNOR staining.

Literature survey for risks arising from the presence of a marker chromosome should be reviewed.

6.5 **Other structural chromosomal abnormalities may observed in prenatal diagnostic**

**Isochromosomes**

An isochromosome is one in which the arms on either side of the centromere are morphologically identical and bear the same genetic loci i.e. one arm is missing while the other is reduplicated (Figure 6.21). Isochromosomes may be formed by,

a.) Horizontal division of the centromere rather than vertical, the two arms of the chromosome being separated instead of two chromatids. In subsequent mitosis the joined arms each act as a bi-armed chromosome.

b.) Formation of isochromosomes may occur by chromatid exchange, or chromatid translocation with a chromosome following breakage, or chromatid translocation within a chromosome following breakage and loss of the distal section of the chromatids. This may cause many isochromosome to be dicentric. Isochromosome
appearing monocentric may have two centromeres so close to each other that they cannot be perceived as separate; special staining may be required to visualize them.

The isochromosome of the long arm of the X chromosome, denoted as i(Xq), is the most commonly seen isochromosome, observed in some individuals with Turner’s syndrome. Isochromosome 17q is seen in some leukemia patients; those having solid tumor may also show isochromosomes. Isochromosomes have also been seen in chromosome 12, 13, 18 and 21. The clinical effects manifested by isochromosome result due to the monosomic state of the missing loci as well as due to the trisomic state of the genes on the isochromosome (Wolf, 1996).

Isochromosomes

Ring Chromosomes

Ring chromosomes are a result of joining of the sticky ends caused by two breaks in a chromosome. The two terminal fragments are lost giving rise to the monosomic state of these loci (Figure 6.22). The monosomy causes the clinical manifestations. If the centromere is within the ring the fragments lost are acentric. Disjoining of ring chromosomes at anaphase may pose a problem especially when a twist is developed in a ring through breakage and reunion. Breakage
and fusion may form larger and smaller rings. Because of mitotic instability, ring chromosomes may be seen only in a proportion of cells. Ring chromosomes have been detected for every human chromosome. Presence of a ring of any type can lead to ring syndrome because of the random duplication and deletion of genetic material in many different cell lines.

Ring chromosomes

(Figure- 6.22)

Dicentric Chromosomes
A dicentric chromosome possesses two centromeres resulting from the joining of two broken fragment of chromosomes, each having a centromere (Figure- 6.22). These may be formed two different chromosomes as in Robertsonian or from two chromatids of the same one as in an isochromosome. The two centromeres may be inactivated in this case. If the centromere are far apart or if both are active, they can be drawn to opposite poles of the spindle, resulting in formation of an anaphase bridge, a chromosome that makes a bridge between two daughter cells.

Dicentric Chromosomes

(Figure- 6.22)
at anaphase. This may cause the dicentrics to be left outside both the daughter nuclei as they form or can break apart and cause loss or gain of chromosomal material. Dicentric chromosomes are most common dicentric and pseudodicentrics are formed from the acrocentric D and G group chromosomes. Other chromosomes might be involved occasionally.

![Dicentric chromosomes](http://ghr.nlm.nih.gov/handbook/illustrations/dicentric)

**Dicentric chromosomes (Figure- 6.22)**

**Polyploidy**

Postzygotic error can lead to diploid/triploid mosaicism and is seen in the vanishing twin’s syndrome. Triploidy is seen commonly in 1st trimester abortion and in pregnancy up to second trimester. A heteroploid cell can arise due to endo reduplication i.e. chromosomal replication with out subsequent cell division and is mostly a cultural artifact.
Abnormal ultrasound findings are most common indication where rapid karyotyping is request for management. If the fetus has abnormalities of classical syndrome e.g. IUGR, choroid plexus cysts, real or cardiac malformations suggestive of trisomy 18 on ultrasound scanning, and on placental biopsy, if the karyotype result is normal, this could be a false negative result. In this case, fetal tissue analysis should be done to confirm the karyotypic pattern.

At any time if a chromosomal rearrangement is detected in prenatal diagnostic sample, paternal karyotype should be done on an urgent basis. For further pregnancy management in case of all fetal tissue samples, which show abnormal chromosomal pattern, prenatal karyotype should be considered to detect the sporadic or familial origin of the same. This can help in recurrence risk estimation.