NEET SS OBG
FETAL MEDICINE

CONTENT

INVERTING THE PYRAMID OF ANTENATAL CARE

Introduction 00:00:17

History :

In early 20th century, hospitalised antenatal care came into action in UK.
In 1930 UK ministry of health passed a memorandum on antenatal clinics : Their conduct and scope. London, His majesty's stationery office, 1930.

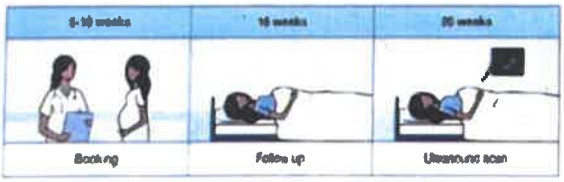
Recommended schedule :

In 1930 :

Gestational age.	Frequency of visits.
Upto 28 weeks.	Every 4 weeks.
28-36 weeks.	Every 2 weeks.
After 36 weeks.	Every 1 week.

In 2023 :

Gestational age.	Frequency of visits.
Upto 28 weeks.	Every 4 weeks.
28-36 weeks.	Every 2 weeks.
After 36 weeks.	Every 1 week.



ANC visit (2023).

ANC visits are more frequent in the second and third trimester because :

- most maternal complications and fetal anomalies are evident at this stage (Acceptable reason).
- most complications cannot be predicted and anomalies cannot be detected early : This is challengeable due to the recent revolution in ANC treatment.

First trimester scan 00:04:16

Integrated evaluation of pregnancy in first trimester including combined evaluation detects most of the major anomalies and defines patient specific risks for most complications.

Combined evaluation includes :

1. maternal demography : Age, race, body mass index (BMI).
2. Biophysical tests.
3. Biochemical tests.

First trimester scan :

Synonymous to NT (Nuchal Translucency) scan, done at 11-14 weeks.

Other uses of first trimester scan :

- Dating the pregnancy.
- Aneuploidy screening.
- Screening of fetal structural anomalies.
- Assessment of chorionicity.
- Screening maternal complications like preeclampsia and still birth.
- Screening fetal complications like IUGR (Intrauterine growth restriction).

Gestational age assessment : 00:08:04

The indication for first trimester scan is gestational age assessment.

Best tool is crown rump length (CRL) and not LMP (Last menstrual Period).

At 10-12 weeks.

Isuog.org guidelines for timing for first trimester scan :

- No reason to offer routine ultrasound simply to confirm an ongoing early pregnancy in the absence of any clinical concerns, pathological symptoms or specific indications.
- It is advisable to offer the first ultrasound scan when gestational age is thought to be between 11 and 13 + 6 weeks gestation, as this provides an opportunity to confirm :
    i. Viability.
    ii. Establish gestational age accurately.
    iii. Determine the number of viable fetuses.

Accurate dating is critical as it influences every decision in pregnancy.

Aneuploidy screening : 00:10:59

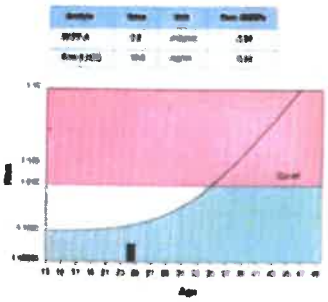
First trimester :
- Double test.
- NT based screening.
- Combined test.
- 1st T Quad.

Second trimester :
- Triple test.
- Quadruple test.
- Genetic sonogram.

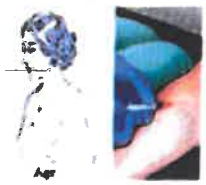
Combined :
- Integrated test.
- Sequential screening.
- Contingent screening.

First trimester aneuploidy screening :

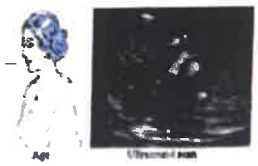
1. Double test : maternal demography + serum markers (β HCG and PAPP-A).



Serum markers.



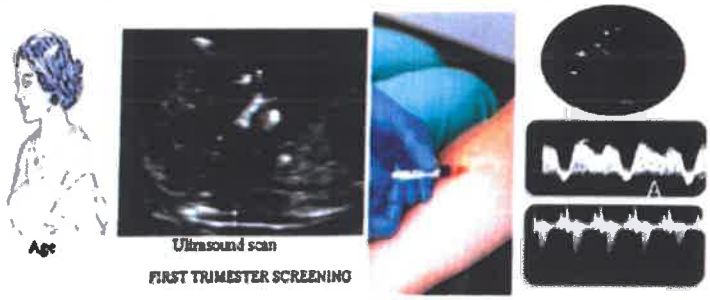
Double test.



NT based screening.

2. NT based screening : maternal demography + NT scan.

3. Combined test + additional markers : maternal demography + NT scan + bio chemical markers + biophysical markers (Nasal bone, ductus venosus, tricuspid regurgitation).



Combined tests + additional markers.

4. Quadraple test :
- maternal demography.
- Serum biochemical markers : β HCG, PAPP-A, PLGF, AFP.

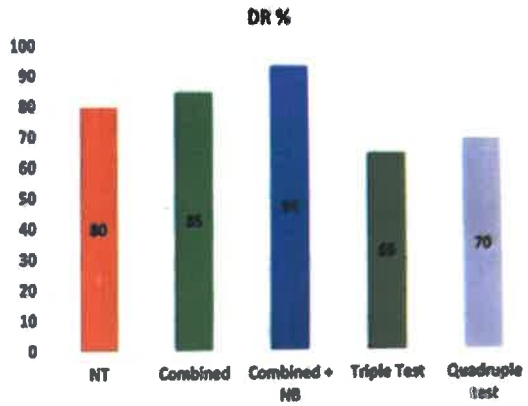
Second trimester tests :

Triple test : AFP + unconjugated estriol (E3) + HCG.

Quadraple test : AFP + unconjugated estriol (E3) + HCG + inhibin.

Note : First trimester screening tests have the best detection rates.

Screening method	Detection of T21%. (FPR - 3%)
Double test.	50.
NT.	70.
Combined test.	80.
Combined tests + additional markers	92 - 95%.
Triple test.	60.
Quadraple test.	65.
Quadraple + Contingent anomaly.	80.
Sequential screening.	90.
Integrated.	93.



Detection rate of various tests.

Anomaly detection

00:14:22

Detection rate of anomalies :

Author	Gestational age (weeks)	Number	Prevalence	Detection rate
Hemadi & Torocsik.	11.	3991.	64(16%).	35(55%).
Economides & Brathwhaite.	12-13 weeks 6 days.	1633.	17(10%).	11(65%).
Ottavo et al.	14.	4076.	88(2.5%).	54(61%).
Carvalho et al.	11-14 weeks.	2853.	130(4.6%).	29(22%).
Taipale et al.	13-14 weeks.	4855.	33(0.7%).	6(18%).

meta analysis (Rossi et al 2013) :

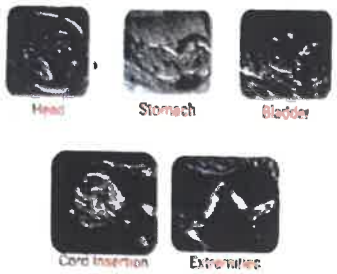
- 19 studies.
- 78,002 fetus.
- Overall detection rate : 51 %.
- When transvaginal scan was added : 64%.

Anomalies in first trimester :

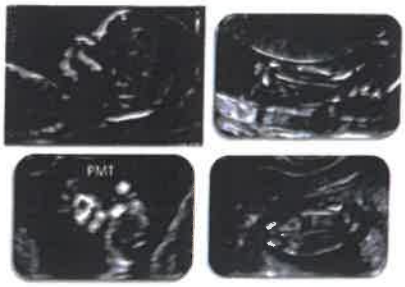
Always detectable	Potentially detectable	Undetectable
Anencephaly.	Posterior fossa defects.	microcephaly.
Alobar holoprosencephaly.	Spina bifida.	ACC.
Body stalk anomaly.	Facial cleft.	Ventriculomegaly due to infection, hemorrhage.
Omphalocele.	Cardiac defects.	Fetal tumours.
Gastroschisis.	Renal defects.	Fetal ovarian cysts
megacystis.	Limb defects.	CCAM, Sequestration.
		Duodenal obstruction, small bowel obstruction.

Isuog.org guidelines :

- If we scan the mandatory anatomical structures (Head, stomach, bladder, cord insertion and extremities), we can diagnose the "always detectable" anomalies in the scan.
- On scanning the extended anatomical structures like facial profile, pre maxillary triangle, kidneys and spine, "potentially detectable" anomalies can be detected.

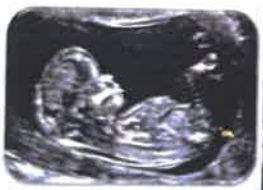


Mandatory anatomical structures.

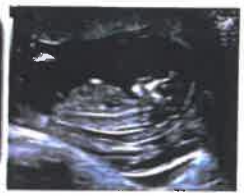


Extended anatomical structures.

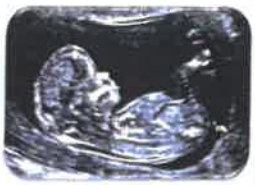
- Anomalies in 1st trimester can be detected by comparing with normal CRL picture :



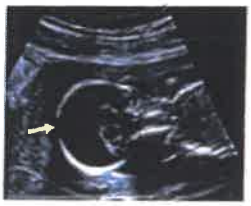
Normal CRL.



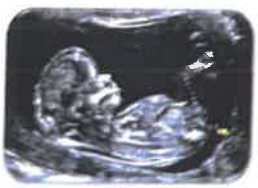
Anencephaly.



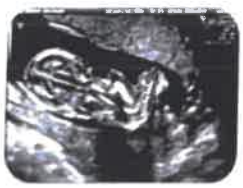
Normal CRL.



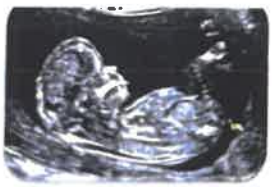
Alobar holoprosencephaly.



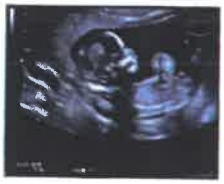
Normal CRL.



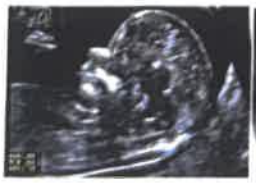
Body stalk anomaly.



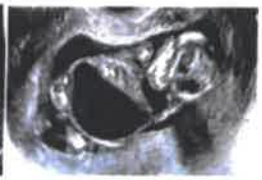
Normal CRL.



Omphalocele/ gastroschisis.



Normal CRL.



Megacystis.

Prediction of maternal fetal complications

00:21:24

ASPRE trial :

Prospective multicentric trial :

N=26,941; conducted in 2 parts.

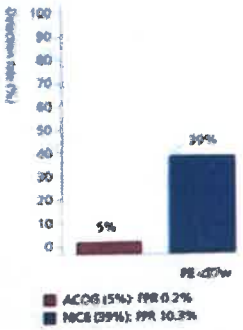
PART 1 :

APSRE trial : Performance of screening for preterm pre-eclampsia.

Perform combined pre eclampsia screening for all pregnant women at 11 - 13+6 weeks : Pregnant women with high risk for pre eclampsia are picked up for part 2 after screening.

Combined pre eclampsia screening include :

1. Maternal demography.
2. Biophysical markers : mean arterial pressure, uterine artery pulsatility index (PI).
3. Biochemical marker : PLGF (Placental growth factor).



Detection rate in PART 1.

NICE guidelines : Detection rate is 39%.

ACOG guidelines : Detection rate is 5%.

Multimodal screening based on fetal medicine foundation : Detection rate is 77%.

PART 2 :

High risk patients from part 1 screening is picked up and divided into 2 random groups → One group is given aspirin 150 mg and the other group is given placebo.

Aspirin :

- Dose : 150mg/day → Aspirin resistance is 30% at 81 mg, 5% at 150mg.
- Start : 12 weeks → Placentation unaffected beyond 16 weeks.
- Stop : 36 weeks → Potential hemorrhage in the neonate.
- Time : Bedtime → Lower preeclampsia, fetal growth restriction, preterm birth, intrauterine death.

Prevention rates of preeclampsia with aspirin :

- 5% in pregnant females ≥ 37 weeks.
- 62% in less than <37 weeks.
- 82% in <34 weeks.
- 11% in <32 weeks.

Multifetal pregnancy

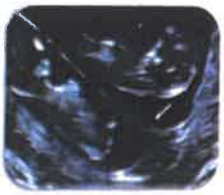
00:27:56

Evidence based facts :

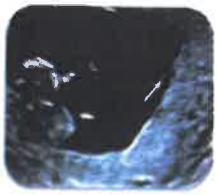
- Best time to determine chorionicity by USG : First trimester of pregnancy

(11-14 weeks).

- Lambda sign : Seen in 100% of dichorionic twins at 10-14 weeks.
- Sensitivity and specificity for determining monochorionicity : 100% and 99.8%, respectively.
- First trimester scan is the best time to label pregnancies when the membrane insertion close to the cervix is seen.



Lambda sign.



T sign.

- Sac A is the sac overlying the cervix and sac B is the sac seen away from the cervix.

Inverted pyramid of antenatal care

00:30:56

Patient specific risk :

At the end of 14 weeks based on the investigations done in the first trimester : Patient can be triaged into low and high risk.

Inverted pyramid of antenatal care :

- Increased frequency of ANC visit in first trimester leads to risk categorisation in patients.
- In later trimesters of pregnancy, patient is given specialised care and has fewer visits in the second and third trimester.
- Complications in pregnancy are avoided by assessing the risk in early period of pregnancy.

Inverted pyramid.

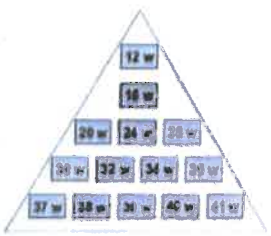
Limitations :

It depends on :

- Good quality first trimester USG scan centre.
- Quality of the lab for which biochemical samples are sent.

This can be overcome by :

- Training properly.
- Tie up with the specialised person/centre.



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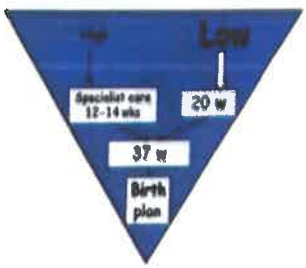


2018.

PRENATAL SCREENING & DIAGNOSIS OF ANEUPLOIDY

Introduction :

Prenatal screening is done to mainly r/o :

1. Down syndrome.
2. Edwards syndrome.
3. Patau syndrome.
4. Other aneuploidies.
5. Preeclampsia risk of preterm birth, fetal demise.

Sir Gregor Johann Mendel

Historic contributions :

Sir Gregor Johann Mendel :

- Discovered laws of inheritance.
- For monogenic disorders.
- Not a/w aneuploidies.

Sir John Hilton Edwards.

Sir John Hilton Edwards :

- Described Trisomy 18 (Edwards syndrome).
- Obvious abnormalities on USG.

Sir Langdon down.

Sir Langdon Down :

- Described Trisomy 21 (Down syndrome).
- No obvious early abnormalities on USG.

Down syndrome : Screening

00:11:55

Features :

- Intellectual disability > 95%.
- CHD 30 to 40%.
- GIT atresias 20%.
- Hypotonia.
- Learning disabilities.
- Alzheimer's disease.
- Leukemia (15 to 20x risk).

Trisomy 21.

Note :

- 50% of fetuses are viable.
- 60% can be structurally normal.
- Ultrasound alone cannot pick up all Down Syndrome with accuracy.
- Incidence of Down 1 : 600
- Life expectancy for people with down syndrome has increased dramatically from 25 years in 1983 to 60 years today.

Strategies of prevention :

Primary prevention :

- Avoid late pregnancies.
- Pre implantation diagnosis.

Secondary prevention (Informed choice) :

- Screening : CVS/amnio if screen positive.
- Option of termination if found affected.

Risk of down syndrome with age :

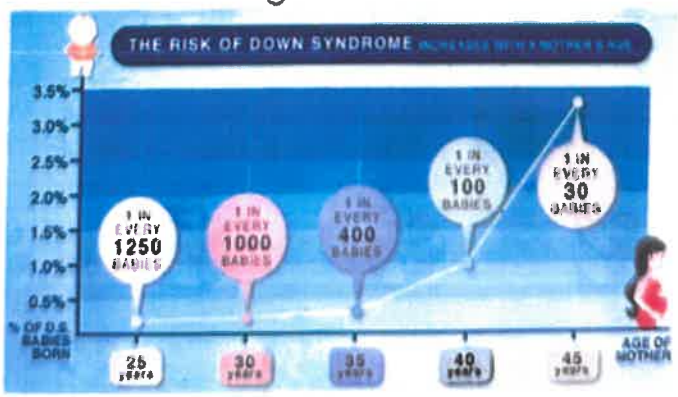
- more prevalent among mothers of older age.
- Exponential rise in prevalence beyond 35 yrs of age.
- Advanced maternal age : Strongest epidemiological link.
- 0.6 to 41 per 1,000 between age 15 and 45.

Genotype surprise :

i) 95% are trisomy 21 d/t gametocyte accidents : Not able to predict, hence universal testing irrespective of age.

ii) 1% mosaic down syndrome.

iii) 4 to 5% translocation down syndrome.



Note :

AIIMS pediatrics cohort → 842 cases

67% occurred in women <35 years.

D/t early completion of family in our indian culture before 35 years.

Ideal scenario testing :

Definitive diagnosis to all pregnant woman given by karyotyping.

i. Invasive technique since fetal tissue required.
ii. Risk of miscarriage.
iii. Expensive.
iv. more practical approach required : Based on personalised risk for aneuploidy.

Concept of screening :

Filtering out most of the normals and filtering in most of the abnormals.

Filters :

i. Maternal age.
ii. Maternal Serum Biochemical markers.
iii. Fetal ultrasound markers.

Terminologies :

Marker :

Anything that is found more frequently in fetuses suspected with a particular condition than in normal fetuses and therefore helps pick up the condition.

Eg : Absent nasal bone in down syndrome.

Apriori risk :

Every woman has some risk that her fetus may be affected by a chromosomal defect.

Apriori probability :

- maternal age (Higher age, higher risk).
- Gestational age (CRL /BPD/FL) : Higher gestational age, lesser risk.
- maternal demography.

mom = Patient's result/median result.

Likelihood Ratio of a given marker :

i) LR of a given marker : Incidence of the marker in trisomy 21 pregnancies/ incidence in chromosomally normal pregnancies.

ii) LR of a given marker : % of chromosomally abnormal fetuses with the marker/% of chromosomally normal fetuses with the marker.

- Positive LR : The number of times the presence of the marker increases the likelihood of DS
- Negative LR : The number of times the absence of the marker decreases the likelihood of DS.

Eg :

EICF :Found in 28.2% of trisomy 21 fetuses and in 4.4% normal fetuses

- Positive LR : 6.41 (28.2 / 4.4)
- Negative LR : 0.75 (71.8 / 95.6).

EICF increases the apriori probability by a factor of 6.41

Absence of this marker reduces the risk by 25%.

Inference :

LR >1 : Test result is associated with the presence of disease.

LR <1 : Test result is associated with the absence of disease.

LR = 1 : Little practical significance.

SPR and FPR.

Screen positive & false positive rate are almost identical if done in large sample.

97% of SPs are FPs

Demographic pretest data :

Factor	modification
maternal weight	• Serum marker values lower in heavier women.
Afro carribean race	• AFP ↑20% • HCG ↑10% • PAPP-A ↑60%
IVF Pregnancies	• Dating, HCG inj, Donor age. • HCG ↑10% • uE3, PAPP-A ↓10%
Type I DM	• AFP, uE3 ↓6 to 8%
Previous Downs	• Apriori probability.
Smoking	• Inhibin ↑60% • PAPP-A, HCG ↓20%

Screening design :

Apriori probability → Screening → Absolute values → mom → Likelihood ratios → Apriori probability x LR = Post test probability.

For multiple markers : Apriori risk x Composite LR = Patient specific risk for down syndrome.

Screening models

00:00:19

- Age based screening.
- NT based screening.
- Double test.
- Combined test.
- Additional USG markers.

} First trimester (Best for screening).

- Triple test.
- Quadruple test.
- Genetic sonogram.

} Second trimester.

- Integrated test.
- Sequential screening.
- Contingent screening.

} Third trimester.

Relative efficacy :

Fixing FPR & comparing detection rate (DR) more effective than fixing DR & comparing FPR.

First trimester screening :

- Only maternal age : 30% detection rate.
- Double test (maternal age + S. biochemical markers) : 50% detection rate.
- Combined test (Double test + NT scan) : 85% detection rate.
- Combined + additional markers (Nasal bone, TR, DV abnormalities) : 92-95%.

markers in 1st trimester :

- hCG
- PAPPA-A

} Placental product.

Timings :

- 11 to 13weeks + 6d
- CRL 45 to 84 mm
- Ideal : 12 to 13 weeks

Risk cut off : 1 in 250.

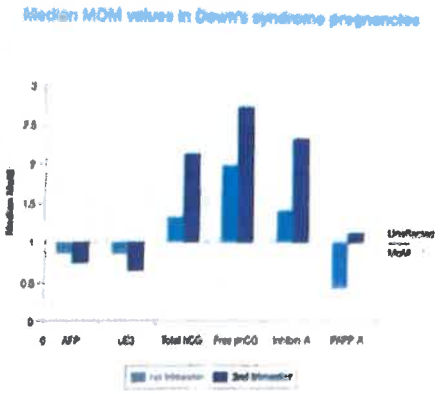
Second trimester screening :

markers :

1. AFP secreted by fetal liver.
2. Ethiny estradiol (EE3) secreted by fetal adrenal.
3. hCG & inhibin by placental products.

Triple test (AFP + EE3 + hCG) : DR 60%

Quadruple test (AFP + EE3 + hCG) : DR 65%



moms for down syndrome.

Timings :

- 15 to 21 weeks.
- BPD : 31 to 52 mm.
- Ideal : 16 to 18 weeks.
- Risk cut off 1 in 250.

Note :

- Decreased fetal products & increased placental products : Down syndrome.
- Only placental product decreased in down syndrome : PAPP-A.
- Trisomy 18 : ↑ Free beta hCG & ↓ PAPP-A
- Trisomy 21 : ↓ Free beta hCG & ↓ PAPP-A

Genetic sonogram :

AKA Level 2 targeted anomaly scan.

Meta-analysis of second trimester markers for trisomy 21

Marker	DR	FPR	LR + ve	LR − ve	Isolated marker
Cardiac echogenic focus	24.4	3.9	5.6	0.80	0.95
Ventriculomegaly	7.5	0.2	27.5	0.94	3.81
Increased nuchal fold	26.0	1.0	23.3	0.80	3.79
Echogenic bowel	16.7	1.1	11.4	0.90	1.65
Mild hydronephrosis	13.9	1.7	7.6	0.92	1.08
Short humerus	30.3	4.6	4.8	0.74	0.76
Short femur	27.7	6.4	3.7	0.80	0.61
ARSA	30.7	1.5	21.5	0.71	3.94
Absent or hypoplastic NB	59.8	2.8	23.3	0.46	6.58

No markers LR 0.13 = 7.7 fold reduction

Meta-analysis 47 studies 1995–2012

markers of and trimester for downs.

Third trimester screening :

Integrated screening :

- Combined test done at 1st trimester (Not release the result) + Quadruple test at second trimester.

- After that report is given; Detection rate is 93%.
- Disadvantage : Failure to return for and blood test.

Contingent screening :

Test result is given after combined test.

Combined test result :

i) High : Do direct test.

ii) Low : No testing further.

iii) Intermediate : Do qauadruple test.

Quadruple test result :

i) High : Do direct test.

ii) Low : No testing.

iii) Intermediate : Do direct test.

Sequential screening :

- 2 stages : Risk given at each stage.
- Screen –ve group offered the second test.
- Post risk of the first becomes apriori risk of the second.
- DR : 90%

Screen method	Detection of T21% (FPR 3%)
Double test	50
NT	70
Combined test	80
Additional markers	92 to 95
Triple test	60
Quadruple test	65
Quadruple + contingent anomaly	80
Sequential screening	90
Integrated	93

Aneuploidy screening methods.

Note :

First trimester screening allows :

i) Early diagnostic testing by CVS possible.

ii) Optimum time for NIPT.

iii) Option of first trimester termination.

Ideal timing for 1st trimester screening :

i) Biochemical markers clearer before 11 weeks.

ii) Anatomical markers clearer after 14 weeks.

iii) Hence it is best to screen at 12 to 13 weeks.

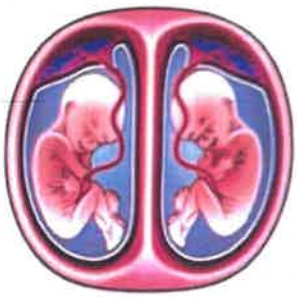
Place for screening :

- Accredited lab with software.
- Quality control on a daily basis.
- Regular audit.

Screening in multiple pregnancies :

First trimester :

- NT & Serum markers can be used.
- Performance of serum markers poorer.
- Establish chorionicity :
  - i) Monochorionic twins are monozygotic : Identical risk for each fetus.
  - ii) Dichorionic twins mostly dizygotic : Separate risks for each fetus.



DCDA twins.

Second trimester :

- Serum markers alone.
- Less accurate than that in singleton pregnancies.

Triplets and higher order multiplies :

Risks based on ultrasound markers alone.

Note :

Always combined test f/b NIPT (Non invasive prenatal testing).

NIPT is never done as first line except in

i) maternal age 38 years or older.

ii) USG findings indicating an increased risk of aneuploidy.

iii) History of a prior pregnancy with a trisomy.

Screening in IVF pregnancies :

- Dating.
- hCG injections : Screening test should not be done within 5 days of injection.
- Donor cycles : Donor age determines the apriori risk.

Test interpretation :

- 1 : 250 high risk : Counselling & offer invasive testing.
- 1 : 250 low risk : Regular AN follow up.
- 1 : 250 to 1 : 1000 : Counselling & NIPT.