Mini Review
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Screening for down syndrome

Introduction

Congenital fetal malformation is important cause of perinatal morbidity &mortality. There is psychological, social & economic burden to parents & society if they survive. Moreover delayed child birth in modern era shortens the reproductive window & increases the risk. Advances in prenatal diagnosis & therapy have enabled us for early diagnosis & safe termination when indicated. Down syndrome being most common nonlethal trisomy thus forms the focus of most genetic screening & testing protocols. Down syndrome was first described by J.L.H. Down in 1866 and 100yrs. later, it was discovered to be caused by Trisomy 21. It Occurs overall in 1 in 800 to 1000 newborn-8% conceptus aneuploidy & accounts for 50% 1st trimester abortion & 5-7% of still births,neonatal deaths. Exact cause is unknown, this mostly results from meiotic non-disjunction and there is evidence of folic acid metabolism abnormalities. The salient features are: Risk increase with maternal age, fetal death rate 30% b/w 12-40weeks, epicanthal folds with up slanting palpebral fissure, flat nasal bridge, small head with flattened occiput, marked hypotonia with tongue protrusion, loose skin at the nape of neck, short fingers, single palmar crease, hypoplasia of middle phalanx of fifth finger, sandal toe gap, cardiac anomalies, GI anomalies, increased risk of leukemia & thyroid disease and IQ-25%-50%.

Tests for fetal aneuploidy

Screening tests

i. Provide an assessment of the risk of having a condition.

ii. Includes Genetic sonogram & Maternal serum markers.

Diagnostic tests includes

a. Chorionic villus sampling.

b. Amniocentesis.

c. Fetal blood sampling.

d. Fetal tissue biopsy.

i. Determine if the condition is present or not.

ii. Carry risk to the pregnancy.

iii. Reserved for subjects testing positive with screening test.

Need for screening

i. All pregnant women are at risk of carrying fetus with genetic abnormalities.

ii. ACOG (2007b) recommends that all pregnant women to be offered screening when presenting before 20weeks.

iii. Down syndrome being most common nonlethal trisomy thus a focus of most genetic screening & testing protocols.

iv. Background risk-maternal age, the gestational age, history of chromosomal defect.

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v. 1% recurrence risk in next pregnancy; depends on type of chromosomal defect.

vi. Parental chromosomal studies not necessary unless trisomy was due to unbalanced translocation.

Women with increased risk of fetal aneuploidy

i. Singleton pregnancy & maternal age>35 at delivery.

ii. Dizygotic twin & maternal age>31 at delivery.

iii. Previous autosomal trisomy birth.

iv. Previous 47XXX or 47XXY birth.

v. Patient/ partner carrier of chromosomal translocation/inversion.

vi. History of triploidy.

vii. Some cases of repetitive early pregnancy losses.

viii. Patient/partner has aneuploidy.

ix. Major fetal structural defect by sonography.

Selected down syndrome screening strategies

First trimester screening

Performed b/w 11-13+6week

Maternal serum analyst screening

i. Free beta-HCG -higher (2.0MoM).

ii. Pregnancy-associated plasma protein -A Lower (0.4MoM).

Sonographic evaluation

a. Nuchal translucency.

b. Ductus venosus blood flow.

c. Nasal bone.

d. Blood flow across Tricuspid valve.

Combination of both

Nuchal translucency (NT) measurement

Ultrasonographic measurement of subcutaneous translucent area

b/w skin & soft tissue overlying fetal spine at back of neck is NT. NT increases with CRL b/w 45 & 85mm, 95th percentile for CRL of 45mm (11wk) & 85mm (13wk 6d) are 2mm & 2.8mm resp. When increased (>95th percentile or >3.5mm) increased risk for fetal aneuploidy & other structural anomalies as cardiac, skeletal dysplasia, genetic syndrome & needs detailed work-up.

Nasal bone

Nasal bone is absent in 73% of Down syndrome fetuses. Prevalence of absent nasal bone reflects ethnicity- highest in Africans, NT thickness- increases with NT, CRL-Decreases with GA. Further evaluation is needed in low risk population. ACOG recommends NB assessment to be used only as secondary marker.

Ductal blood flow (other markers)

Increased impedance to flow in ductus venosus is suggested by absent/ reversed a-wave at 11-13week gestation. This may be present in approx. 70% of Down's fetuses and requires skilled operators.

Tricuspid regurgitation

Found in approx 74% of Down's fetuses

Note: NB, abnormal ductal flow, TR can be used as second line screening resulting in major reduction of invasive testing, front omaxillary facial angle (>85degree) is found in 64%.

Second trimester screening

Performed b/w 15-20weeks and includes Triple test/Quad test and or Genetic sonogram.

Triple test

i. MSAFP-lower (0.7MoM).

ii. Free bHCG-higher(2.0MoM).

iii. uE3 (unconjugated estriol)-lower(0.8MoM).

Quad test

i. All above+inhibin A (higher 1.7MoM).

ii. Knowing Accurate gestational age is essential.

iii. ACOG recommends positive screening test result should be offered diagnostic test for karyo typing.

Genetic sonogram

Ideally performed b/w 18-20week. Aneuploidy is often associated with both major anatomical markers & minor markers, reduces invasive testing rate with 75% Detection rate and a false positive rate of 10-15.

Soft signs/minor markers

Along with Nuchal fold thickening (>6mm) it includes nasal bone absence or hypoplasia, shortened frontal bone or brachycephaly, short ear length, echogenic intracardiac focus, echogenic bowel, mild renal pelvis dilatation (AP dia of pelvis>4mm), widened iliac angle, Widened gap between first and second toes-sandal gap, hypoplastic mid-phalanx of fifth digit, single transverse palmar crease, short femur (observed to expected<10 percentile) and Short humerus (observed to expected <10percentile). Sonographic detection of Down syndrome is increased by addition of minor sonographic markers that are collectively known as "soft signs". Incorporation of minor markers into second trimester screening protocols in high risk population has increased detection rate upto 50-75%. In the absence of aneuploidy or an associated major malformation, these minor abnormalities usually do not affect the fetal prognosis. Aneuploidy risk increases with the number of markers identified

Limitations

i. At least 10% of the unaffected pregnancies will have one of these markers and lack of standard measurement criteria.

ii. ACOG recommends risk assessment be limited to specialized centers.

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Conflict of interest

The author declares no conflict of interest.