Indian Journal of Medical Specialities 9 (2018) 86–93

Contents lists available at ScienceDirect

Indian Journal of Medical Specialities

journal homepage: www.elsevier.com/locate/injms

Review article

Screening chromosomal anomalies in early pregnancy: When and why

Ayesha Ahmad[a], Aruna Nigam[b], Saloni Arora[a,*], Smriti Prasad[a]

[a] Apollo Centre for Fetal Medicine, New Delhi, India
[b] Hamdard Institute of Medical Sciences and Research, New Delhi, India

ARTICLE INFO

Article history:
Received 19 April 2018
Accepted 4 May 2018
Available online 5 May 2018

Keywords:
Nuchal translucency
First trimester screening
Down's syndrome screening
Cell free fetal DNA
Quadruple test
Dual test

ABSTRACT

Prenatal screening for aneuploidies is done using maternal serum and sonographic markers. Although many screening tests are available, their correct application still does not have uniformity. This review will give insight into the existing screening protocols, their merits and demerits, interpretation of results and the relevance of these tests in low resource settings. Cell free fetal DNA and its exciting role in non invasive prenatal testing along with its advantages and drawbacks is also taken up. We have further considered the role of counseling and its importance before embarking on the screening tests. The upcoming role of maternal serum markers for prediction of adverse obstetrical outcomes is also discussed.

Contents

* Corresponding author.
E-mail addresses: docayeshaahmad@gmail.com (A. Ayesha), prakasharuna@hotmail.com (N. Aruna), saloni.arora09@gmail.com (A. Saloni), drsmritiprasad20@gmail.com (P. Smriti).

https://doi.org/10.1016/j.injms.2018.05.004
0976-2884/

1. Introduction

The past few decades have witnessed identification of many biochemical substances in maternal serum which are produced by the feto-placental unit. Some of these have been found to be associated with fetal aneuploidies and structural abnormalities. Prenatal screening for aneuploidies based on ultrasound and biochemical markers in maternal serum has been one of the major breakthroughs in antenatal care in the past century. The aim of screening is to assess if a woman is at increased risk of having a baby with a genetic disorder.

This review will give insight into the biochemical markers which are currently being utilized in prenatal screening. It will also discuss current screening protocols without delving into anomaly scan.

2. Data identification

The Cochrane Library, Medline and PubMed electronic databases were searched for original articles and standard guidelines issued by different obstetrical bodies. The search was restricted to articles from 2000 to January 2018 and the English language. The databases were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search. Search words included 'nuchal translucency', 'cell free fetal DNA', 'quadruple test', 'down syndrome screening' 'NIPT' and was limited to humans.

3. Biochemical screening for aneuploidies

Trisomy 21 comprises approximately half of the major aneuploidies detected prenatally. The next most common autosomal trisomies are trisomy 18 and trisomy 13. Together, they make up about 80% of major aneuploidies detected by prenatal diagnosis [1].

Biochemical screening for aneuploidies can be done either in the first or second trimester of pregnancy. The maternal serum values are measured and reported as multiples of median [MoM] of the unaffected population. First trimester risk assessment is based on a combination of maternal age, maternal serum free beta human chorionic gonadotropin [b-hCG], pregnancy associated plasma protein A [PAPP-A] and fetal nuchal translucency thickness at 11 to 13 + 6 weeks. The detection rate [DR] for various fetal aneuploidies varies from 74%–93% with a fixed false positive rate of 5% [2–5] (Table 1).

DR is higher for those aneuploidies which are associated with major structural defects such as holoprosencephaly, cystic hygroma etc. because the ultrasound features are pathognomonic and enable easier detection as compared to those conditions which have minimal sonographic soft markers.

Second trimester screening is done at 15–20 weeks of gestation by combining maternal serum values of alpha fetoprotein [AFP], hCG, unconjugated estriol [uE3] and inhibin A. This has a sensitivity of 81% for detection of Trisomy 21, with a 7% false positive rate [8].

3.1. Sonographic screening of aneuploidies in first trimester

'Nuchal translucency' [NT] was coined by Nicolaides and colleagues in 1992 when they found an increased translucent region behind neck of fetuses diagnosed with aneuploidy on chorionic villous sampling (CVS).They proposed NT as a sonographic marker for aneuploidy screening. The findings were corroborated by other investigators and the NT model was validated for first trimester screening of chromosomal abnormalities. NT increases with gestational age and its accuracy as a marker for aneuploidies decreases with gestational age (Table 2).

Table 1
Detection rate [DR] of aneuploidies in first trimester by biochemical screening for a false positive rate of 5% [6,7].

Aneuploidy	DR
Triploidy, Monosomy X, Trisomy 13, Trisomy 18	94%
Trisomy 21	90%
Deletions, partial trisomies, unbalanced translocations and sex chromosomal aneuploidies besides monosomy X.	60%

Table 2
DR of aneuploidies by first trimester NT with a fixed false positive rate of 5% [9].

Period of gestation [in weeks]	DR [in %]
11	87
12	85
13	82

In order to standardize results, NT is converted into multiples of median [MoM] for gestational age and risk determined using either 95th percentile for MoM or the delta value of the observed NT from one expected for the crown-rump length. However, an NT of greater than 3 mm is universally accepted as enlarged and considered an indication for diagnostic testing as the risk of aneuploidy exceeds 1 in 6 at this threshold regardless of gestational age correction.

Recently, in addition to NT, reversed flow in ductus venosus [DV], tricuspid regurgitation (Fig. 1) and absence of nasal bone (Fig. 2) have been found to increase effectiveness of trisomy 21 screening [9].

3.2. Nuchal translucency measurement

NT measurement can be subject to large inter-observer variation if not performed under a stringent protocol. Strict guidelines (Fig. 3) for NT measurement have been issued by Fetal Medicine Foundation, which provides NT training and certification to ensure maintenance of high quality programs for first trimester screening. The Nuchal Translucency Quality Review [NTQR] program is another organization which trains sonographers for NT measurement.

3.3. Maternal serum analytes in first and second trimester aneuploidy screening

From a multitude of biochemical markers investigated, five have emerged as relevant in aneuploidy screening.

- Maternal Serum PAPP-A

PAPP-A is a glycoprotein produced by placental syncytiotrophoblast, detectable in plasma of pregnant women. It increases the bioavailability of insulin-like growth factor [IGF], modulates glucose and amino acid transport across placenta and plays a pivotal role in trophoblast invasion, early development and vascularisation of placenta and placental bed. Low levels of PAPP-A are associated with low levels of free IGF.

The concentration of PAPP-A in maternal circulation increases exponentially with gestation which causes interpretation of a given value to be very dependent on gestational age. PAPP-A has a positive relationship with birth weight and a low PAPP-A is also associated with adverse fetal outcomes especially those that may involve abnormal trophoblastic invasion such as preterm delivery and hypertensive disease of pregnancy [11,12]. Maternal PAPP-A <0.4 MoM is a major risk factor for small for gestational age [SGA] fetus [13].

- Maternal serum free b-hCG

Human chorionic gonadotrophin [hCG] is a glycoprotein hormone produced by syncytiotrophoblasts [14]. It is instrumental in initiation and maintenance of pregnancy by mediating