SECOND TRIMESTER MATERNAL SERUM SCREENING PROGRAMMES FOR THE DETECTION OF DOWN'S SYNDROME

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BIRTH OF A DS INDIVIDUAL

- Is a psychological shock for the parents
- Costs a lot to the society
- Hence, the importance of early prenatal diagnosis.
- The overall risk of having a newborn with DS is 0.13%

Maternal Serum Screening:

-Is a non invasive method aiming to:

- Reduce the number of women undergoing invasive prenatal diagnosis
- Increase the proportion of DS fetuses detected

-It estimates the risk of carrying an affected baby

-It is not a diagnostic test

INVASIVE TECHNIQUES (AMNIOCENTESIS, CVS)

- Offer definitive diagnosis
- Bear the risk of fetal loss
- Are expensive
- Therefore, cannot be offered to all women

STEPS OF SCREENING

- The best time : 15 - 20 weeks gestation.
- Women evaluated as having a high risk of giving birth to a DS baby can be identified and offered confirmatory testing using an invasive technique.
- Parental counselling is essential to insure informed consent to further investigation and for any termination of pregnancy that may result.

AGE - RELATED RISKS AND SCREENING

- The first screening programmes relied upon amniocentesis, offered only to women over 35 years of age, thus detecting only 20 % - 30 % of all DS, the rest being born to younger women.
- By using the age of 35 years or older as the criterion for prenatal screening, most of the cases remain undetected because their age - related risks are lower than the risk of a pregnancy loss caused by amniocenteseis.

PRINCIPLES OF SCREENING

- A cut - off risk is selected
- The detection rate represents the sensitivity
- The false positive rate assesses the specificity
- The values of the markers are expressed in MoM
- Every lab must determine medians of its own
- Correct gestational dating is essential
- A follow - up study should be performed
- The final risk is affected by several factors

MATERNAL SERUM SCREENING RELIES UPON:

- The combination of age-related risks and the levels of several biochemical markers. The principal markers are:
- -AFP
- -hCG
- -Free beta - hCG
- -uE3

AFP

- Decreased levels of MSAFP (about 72 % of normal values) are associated with trisomy 21, independent of maternal age
- Because of the extensive overlap of normal and trisomic distributions, selection of a cut - off corresponding to any detection rate will result in false positives.
- The combination: age + MSAFP gives a detection rate of 25% - 33% at a false positive of 5%

hCG

- Increased levels of hCG (1.94 - 2.03 MoM of normal pregnancy levels) are associated with DS.

- Using maternal age and hCG levels, at a cut - off risk of 1 : 380, the detection rate varies from 55% - 60% at a false positive from 6.7% - 8.5%.

uE3

- Decreased levels of uE3, about 75% of normal values, are associated with trisomy 21.
- uE3 and AFP values are highly correlated.
- Using maternal age and uE3, in a multicentre study, at a cut - off risk of 1 : 380, Spencer found a 45.7% detection rate at a false positive rate of 9.1%.

FREE BETA - hCG

- A geometrical mean MoM maternal serum of 2.06 -2.68 has been reported in DS pregnancies.
- The effectiveness of free beta - hCG is claimed to be superior to that of total hCG.
- The detection effiency is higher earlier in pregnancy (14-17 weeks).
- At a cut - off risk of 1/380, using age and free beta - hCG, a detection rate of 55% - 66.7% at a false positive rate of 5.4% - 8.3% was found.

THESE MARKERS CAN ALSO BE USED TO SCREEN FOR :

1. Neural tube defects
   anencephaly, spina bifida, encephalocele
2. Abdominal wall defects
   omphalocele, gastroschisis
3. Chromosomal anomalies
   trisomy 18
4. Preeclampsia and other complications of pregnancy

OTHER SERUM MARKERS

- Pregnancy - Associated Plasma Protein (PAPP-A)

  In combination with free beta - hCG this marker is under study for first trimester screening.
- Inhibin - A.
- Urea - resistant neutrophil alkaline phospatase.
- Ca-125

SCREENING TEST COMBINATIONS

- Triple tests
  - total hCG, AFP, uE3
  - free beta - hCG, AFP, uE3
- Double test
  - free beta - hCG, AFP
- Which is the best?

QUESTIONS

- Does estriol significantly add to detection ?
- Is free beta - hCG superior to total hCG ?

DOES ESTRIOL ADD TO DETECTION?

- Several conclusions recommend against using uE3 levels as a marker for DS screening.
- Several others still rely on it.
- In fact, there is a correlation between uE3 and AFP values and no significant difference is found in the detection rate between double and triple tests. The double test offers so a lower cost.
- More studies are needed.

FREE BETA - hCG vs. TOTAL hCG

- Many studies conclude that free beta - hCG provides a higher detection rate at a lower false positive rate.
- The detection rate is found up to 82.0% prior to 17 weeks GA, and 70.2% after 17 weeks GA.
- For a fixed false positive rate an 8-10 % higher detection rate can be predicted with free beta-hCG.
- The median concentrations of free beta subunit are higher than those of total hCG in DS cases.

FREE BETA - hCG vs. TOTAL hCG

- The wider separation between the MoM may explain the higher detection rate, making free beta a more discriminatory marker.
- Other authors still use total hCG
- Further studies are needed to know which of these opposing conclusions is going to prevail.

DOUBLE vs. TRIPLE TEST

- The double test increases the detection rate and decreases the false positive rate at a lower running cost. So, if not better , the double test is at least not worse than the classical triple test.

- Since DS cases are rare it takes time for further studies to show definitive conclusions.

FUTURE PERSPECTIVES

- A new screen combining urine analytes and serum AFP is under investigation.

- There are enthusiastic reports on first - trimester screening

FACTORS AFFECTING THE SCREENING

- Gestational dating
- Maternal weight
- Diabetes mellitus
- Race or ethnic group
- Possible genetic predisposition
- Multiple pregnancy
- Possible effect of parity, diurnal variation and smoking

INFORMING THE PATIENTS

- Screen positive results :

  1. The test gives the probability of carrying a DS and not the diagnosis of the anomaly.

  2. It means an increased risk and additional diagnostic tests are offered.

  3. The most common outcome of a screen positive result is a normal baby

INFORMING THE PATIENTS

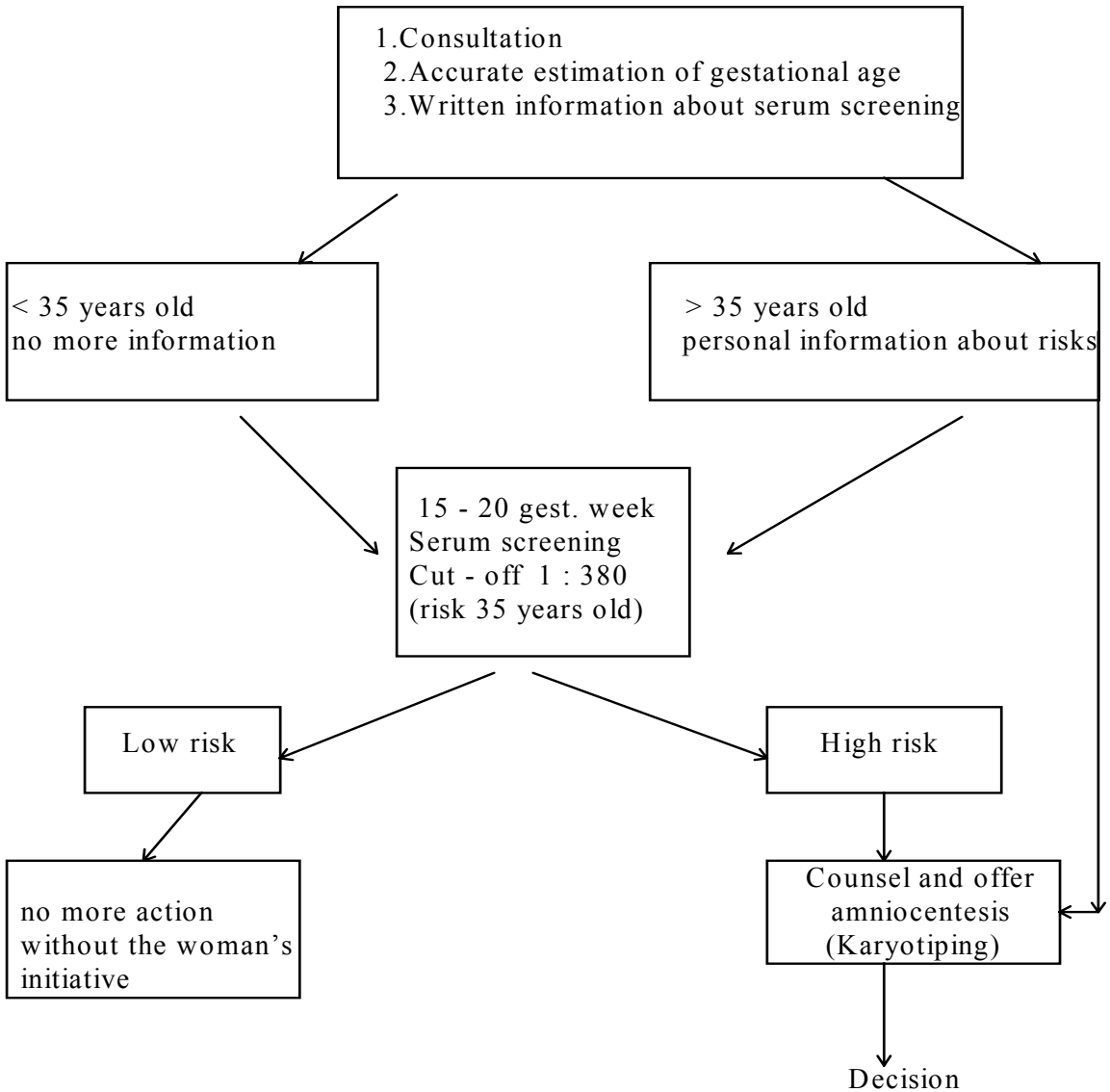
- Screen negative results :

  1. The risk is low enough that a diagnostic test is not counselled.

  2. These screening programmes screen only for certain anomalies. It is not a test for all birth defects and fetal anomalies.

  3. A screen negative result does not guarantee a normal baby.

8. SUGGESTED SCREENING PROTOCOL FOR DOWN'S SYNDROME



CONCLUSION

- The addition of maternal serum markers can improve screening sensitivity for fetal DS.
- The best combination, in addition to maternal age, is found to be free beta - hCG + AFP, but still this remains controversial.
- The information must be individualized since for different patients risk factors are personal. Different cultures and ethics react differently to the philosophy of this screening.

PERSPECTIVES FOR DS SCREENING IN ALBANIA

- DS screening programmes are not available in Albania for the present due to the poor economic status of the country.
- An epidemiological study of DS must be done first. This may help to be aware of the cost the society spends on these individuals.
- A pilot study can then be performed to
  - assess the acceptability
  - provide data on economical benefits
  - improve prenatal care.

FUNDING

- An initial FUND to perform the pilot study would be a great deal of help!