International Federation of Gynecology and Obstetrics

Working Group on Best Practice on Maternal-Foetal Medicine

FIGO Good Practice Advice

1. Screening for chromosomal abnormalities and non invasive prenatal diagnosis and testing

Universal screening is a strategy applied to all individuals of a certain category to identify a high risk group to have an unrecognized disease in individuals without signs or symptoms of such disease (e.g. screening of all pregnant women to identify the high-risk group for fetal chromosomal abnormalities). A test used in a screening program, especially for a disease with low incidence, must have a high detection rate (DR) and low false positive rate (FPR). Prenatal diagnosis of fetal aneuploidies necessitates invasive testing, which is essentially carried out by chorionic villus sampling at 10–15 weeks' gestation or amniocentesis at or after 16 weeks. However, invasive testing is expensive and can cause miscarriage in about 1% of pregnancies; it is therefore reserved for cases identified by screening as being at high-risk for aneuploidies.

First-trimester screening for trisomies 21, 18 and 13 by a combination of maternal age, fetal nuchal translucency thickness (NT), fetal heart rate (FHR) and serum-free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) can detect about 90% of cases of trisomy 21 and 95% of those with trisomies 18 and 13, at FPR of about 5% . The performance of first-trimester screening can be improved by expanding the combined test to include other first trimester sonographic markers, such as the presence or absence of the fetal nasal bone, measurement of fetal ductus venosus pulsatility index for veins (DV-PIV) and regurgitation across the tricuspid valve.

Some countries developed a national program of screening for trisomy 21 based on the combined risk test and the offer of invasive testing at a risk cut-off which aims to maintain the invasive test rate at 3% or less. In others there are no national guidelines on screening and individual practitioners offer a variety of first and/or second trimester methods. Even worse, in some parts of Europe the rate of invasive testing is in excess of 20% based mainly on maternal age.

Recently, screening for fetal aneuploidies based on the analysis of cell free DNA (cfDNA) in the plasma of pregnant women has been introduced into clinical practice . This can be undertaken from as early as the 10th week of pregnancy with results available approximately 1 week after maternal blood sampling. Evidence suggests that analysis of cfDNA in maternal blood can detect about 99% of cases of trisomy 21, 97% of trisomy 18, and 92% of trisomy 13, with respective FPRs of 0.08%, 0.15% and 0.2%.

At present, cfDNA testing is expensive and therefore widespread uptake of the test into routine clinical practice is likely to be contingent on the results of first-line screening by another method, preferably the first-trimester combined test, rather than as a primary method of screening. Such a strategy would also retain the advantages of first-trimester testing by ultrasound and biochemistry, including accurate

pregnancy dating, early detection of many major fetal defects and prediction, with the potential of prevention, of a wide range of pregnancy complications, including preterm birth and preeclampsia.

The International Federation of Gynecology and Obstetrics (FIGO) recommends the following:

1. Maternal age has a low performance as a screening for fetal chromosomal abnormalities with a DR of 30-50% for FPR of 5-20%. Therefore, **invasive testing for diagnosis of fetal aneuploidies should not be carried out by taking into account only maternal age.**

2. First-line screening for trisomies 21, 18 and 13 should be achieved by the combined test, which takes into account maternal age, fetal nuchal translucency (NT) thickness, fetal heart rate (FHR) and maternal serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A). The combined risk test has a DR of 90% for trisomy 21 and 95% for trisomies 18 and 13, at FPR of about 5%.

3. The combined test could be improved by assessing additional ultrasonographic markers, including the fetal nasal bone and Doppler assessment of the fetal ductus venosus flow and tricuspid flow. If all those markers are included the DR is increased to more than 95% and the FPR decreased to less than 3%.

4. Screening by analysis of cfDNA in maternal blood has a DR of 99% for trisomy 21, 97% for trisomy 18 and 92% of trisomy 13, at a total FPR of 0.4%.

5. Clinical implementation of cfDNA testing should preferably be in a contingent strategy based on the results of first-line screening by the combined test at 11-13 weeks' gestation. In this case, we recommend the strategy below:
    - Combined test risk over **1 in 100**: the patients can be offered the options of cfDNA testing or invasive testing.
    - Combined test risk between **1 in 101 and 1 in 2,500**: the patients can be offered the option of cfDNA testing
    - Combined test risk lower than **1 in 2,500:** there is no need for further testing.

    Patients contemplating pregnancy termination following a positive result from cfDNA testing should be advised that the diagnosis **should be confirmed** by invasive testing before undertaking any further action.

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2. Periconceptional folic acid for the prevention of neural tube defects

Neural tube defects (NTD) are severe birth anomalies, due to lack of neural tube closure at either the upper or lower end in the third to fourth week after conception (day 26 to day 28 post-conception).
NTD commonly occur in all population worldwide, especially in the low and middle income countries. Each year, more than 4,500 pregnancies in the European Union are affected by NTD . In the United Kingdom and Ireland, the prevalence of NTD declined from 4.5 per 1,000 births in 1980 to 1.5 per 1,000 in the 1990s In contrast, in the rest of Europe the prevalence during the 1980s and thereafter reminded close to 1 per 1.000 births. In the USA, the incidence ranges from 1.4 to 1.6 per 1,000 live births and 0.8 per 1,000 births in Canada. In the Latin America, the prevalence was about 5 cases per 1,000 births in the Brazil northeastern and South region, and in the southeast, the prevalence was 1 per 1,000 births. In Mexico, the current prevalence is about 1 in 1,000 births.
There are several evidences supporting the hypothesis for the relationship between folate deficiency and NTD, such as: (a) RCT for the prevention of primary occurrence or recurrence has been confirmed that periconceptional acid folic supplementation reduces the rate of NTD with reduction rate of 72%, (b) folic acid antagonists (methotrexate, didhydrofolate reductase inhibitors and others) increase the risk for NTD; and, concentration of folate in red blood cells is lower in women which give birth to children with NTD.
Hence, folic acid supplementation is of great benefit, especially in developing country settings for several reasons. Firstly, the prevalence of NTD in developing countries is very high compared to the industrialised world. Secondly, folic acid supplements are readily available and affordable. Since iron supplementation is almost universally recommended in pregnancy, especially in developing country reproductive health programs, it would be convenient to combine the two interventions. Nevertheless, the keystone is pre-pregnancy administration the synthetic folic acid supplement, which may not be easy in public health programs geared principally towards pregnant women.

The International Federation of Gynecology and Obstetrics (FIGO) recommends that (see also Table):

1. All women who plans to become pregnant or all women at childbearing age without contraceptive method and who do not present risk factors for NTD should utilize 400 micrograms (0.4mg) of synthetic folic acid, beginning at least 30 days before the conception and continue daily supplements throughout the first trimester of pregnancy.

2. All women in the reproductive age group should be advised about the benefits of folic acid supplementation during any medical appointment (e.g., birth control renewal, cervical cancer prevention clinic, yearly examination), especially if they are planning pregnancy in the near future, or they do not use any contraceptive method, or are using a contraceptive method that does not

guarantee an optimal birth control,

3. The health care providers should inform the woman at counseling that:
   a) the benefit of folic acid supplementation is not limited to the reduction of risk of NTD, but include possibly the reduction of risk of other adverse outcomes, including congenital heart defects, orofacial and cleft palate defects, low birth weight, preterm birth, and autism;
   b) the folic acid supplementation of 400 mcg (0.4 mg) can be taken for years, without any known side effects, even in countries with mandatory staple food fortification.
   c) the effects of higher intakes of folic acid are not well known but include complicating the diagnosis of vitamin B12 deficiency; therefore care should be taken to keep total folic acid consumption at less than 1 mg per day, except for women who are at high risk of having a pregnancy affected by a NTD.

4. Women who have risk factors should be advised that synthetic folic acid supplementation at a dose of 4,000 micrograms per day (4.0 mg) is recommended. It should start at least 30 days before the conception and tcontinue as daily supplements throughout the first trimester of pregnancy.

5. The risk factors include women with:
   a. NTD-affected previous pregnancy,
   b. partner affected by NTD
   c. first degree relative which had affected by NTD,
   d. pre-pregnancy diabetes,
   e. epilepsy treatment with valproic acid or carbamazepine,
   f. Use of folate antagonists (methotrexate, sulfonamides, etc)
   g. malabsorption syndrome,
   h. obesity (BMI >35 Kg/m^2),

6. Finally The International Federation of Gynecology and Obstetrics (FIGO) encourages all efforts of public agencies worldwide towards the development of more comprehensive programs to fortify food with synthetic folic acid and more vigilance in monitoring these programs.

Table: Summary of the International Federation of Gynecology and Obstetrics recommendations regarding the administration of folic acid to prevent the NTD.

Population	Women who plan to become pregnant or are at childbearing age **with no** contraceptive method.
Recommendation	Daily supplementation of synthetic folic acid at a dose of 400 mcg.
Time using folic acid	Supplementation should begin at least 30 days before conception and should be maintained for the first trimester of pregnancy.
Risk Assessment for NTD	High-risk factors include: •NTD affected previous pregnancy •Partner affected by *Spina bifida* •First degree relative affected by NTD •Use of anticonvulsants. •pre-gestational diabetes. •Obesity (BMI> 35 kg/m^2). •Use of folate antagonists (methotrexate, sulfonamides, etc.). •Malabsorption syndromes (including pregnant women with a history of surgery for obesity).
Note: The women at high risk group should be instructed to use a daily dose of 4,000 micrograms (4 mg) for the same time recommended above.	
Recommendations from other Associations	The American College of Obstetricians and Gynecologists, the American Academy of Family Physicians, American Academy of Pediatrics, the National Institute for Health and Clinical Excellence (NICE) Guidance and many other organizations have similar recommendations

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3. Cervical length and progesterone for the prediction and prevention of preterm birth

At least 15 million babies are born preterm worldwide each year. Preterm birth-related deaths are one of the leading causes of infant mortality; over one million babies die each year from preterm birth complications. The rates of preterm birth range from 5-18%; over 80% of preterm babies are born between 32 and 37 weeks of gestation. The sequelae of preterm birth include respiratory distress syndrome, necrotizing enterocolitis, neonatal sepsis, neurodevelopmental disabilities, cerebral palsy and neonatal death. Despite decades of research, high rates of preterm birth and infant mortality persist in both developed and developing countries.

A sonographic short cervix diagnosed by transvaginal ultrasound is the most powerful predictor of preterm delivery (50% of women with a cervical length ≤ 15 mm will deliver prior to 32 weeks of gestation). R*andomized clinical trials and systematic reviews have demonstrated that vaginal progesterone reduces significantly the rate of preterm birth by 50 % and reduces neonatal morbidity/mortality*. The use of cervical length screening and vaginal progesterone is cost saving.

The International Federation of Gynecology and Obstetrics (FIGO) recommends the following (see also Table):

1. _Sonographic cervical length measurement should be performed in all pregnant patients at 19 - 23 6/7 weeks of gestation using transvaginal ultrasound. This can be done at the same time as the ultrasound performed for the anatomical survey.
2. Women with a sonographic short cervix (< 25 mm) diagnosed in the mid-trimester should be offered daily vaginal micronized progesterone treatment for the prevention of preterm birth and neonatal morbidity.
3. The progesterone formulation to be used is vaginal micronized progesterone (200 mg vaginal soft capsules) nightly or vaginal micronized progesterone gel (90 mg) each morning .
4. -Universal cervical length screening and vaginal progesterone treatment (90mg vaginal gel or 200mg micronized vaginal soft capsules) is a cost-effective model for the prevention of preterm birth.
5. In cases in which a transvaginal ultrasound is not available, transabdominal ultrasound (with different cutoff) or other devices may be used as a screening

tool to measure objectively and reliably the cervical length.

Table: International Federation of Gynecology and Obstetrics recommendations regarding the use of transvaginal sonographic cervical length and vaginal progesterone use for the prevention of preterm birth.

Population	All pregnant women with a singleton gestation.
Recommendation	Tranvaginal sonographic cervical length measurement at 19 – 23 6/7 weeks for all pregnant patients. Vaginal progesterone administered to women with a cervical length ≤ 25 mm.
200 mg vaginal soft capsules or 90 mg vaginal gel of micronised progesterone can be used for treatment.	
Time using progesterone	Treatment should begin at the time of the diagnosis of a short cervix until 36 6/7 weeks, labor or rupture of membranes.
Risk Assessment	**Transvaginal sonographic cervical length on all patients regardless of obstetrical history.**
Other recommendation	When a transvaginal ultrasound is not available other devices may be used as a screening tool to measure objectively and reliably the cervical length

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THESE ADVICES HAVE BEEN PREPARED BY THE FIGO WORKING GROUP " BEST PRACTICE IN MATERNAL-FOETAL MEDICINE" * AND ENDORSED BY THE FIGO EXECUTIVE BOARD ON JULY 2014

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