



www.figo.org

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

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

FIGO COMMITTEE REPORT

Best practice in maternal–fetal medicine[☆]



FIGO Working Group on Best Practice in Maternal–Fetal Medicine¹

Premise

Recent developments have changed many previous assumptions about the best options for management of pregnancy and childbirth, therefore FIGO aims to provide leadership and clarity for the application of the new (and relatively new) techniques and clinical options that are now available to clinicians for the successful management of the pregnant mother and her fetus/newborn. Although these issues apply universally, they are particularly important in industrialized and semi-industrialized countries, where they are already part of much clinical practice and where, therefore, authoritative guidance is urgently needed to establish best practice.

These FIGO guidelines present best practice advice in maternal–fetal medicine regarding:

1. Screening for chromosomal abnormalities and noninvasive prenatal diagnosis and testing.
2. Periconceptional folic acid for the prevention of neural tube defects.
3. Cervical length and progesterone for the prediction and prevention of preterm birth.

1. Screening for chromosomal abnormalities and noninvasive prenatal diagnosis and testing

Universal screening is a strategy applied to all individuals of a certain category to identify a high-risk group with 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 and low false-positive rate. Prenatal diagnosis of fetal aneuploidies necessitates

invasive testing, which is essentially carried out by chorionic villus sampling at 10–15 weeks of 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, fetal heart rate, 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, with a false-positive rate of approximately 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 have 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 that aims to maintain the invasive test rate at 3% or less. In other countries there are no national guidelines on screening, and individual practitioners offer a variety of first and/or second-trimester methods. More worryingly, 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 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 false-positive rates 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 pre-eclampsia.

FIGO recommends the following:

1. Maternal age has a low performance as a screening tool for fetal chromosomal abnormalities, with a detection rate of 30%–50% and

[☆] Endorsed in July 2014 by the FIGO Executive Board. This advice should not be considered as standards of care or legal standards in clinical practice.

* Corresponding author: Gian Carlo Di Renzo

Department of Obstetrics and Gynecology, Santa Maria della Misericordia University Hospital, 06132 San Sisto, Perugia, Italy. Tel.: +39 075 5783829, +39 075 5783231; fax: +39 075 5783829.

E-mail address: giancarlo.direnzo@unipg.it

¹ Gian Carlo Di Renzo (Chair)*; Eduardo Fonseca, Brazil; Sonia Hassan, USA; Mark Kurtzer, Russia; Maria Teresa Leis, Mexico; Narendra Malhotra, India; Kypros Nicolaides, UK; Huixia Yang, China (members). Sabaratnam Arulkumaran, UK (FIGO President, ex officio); Pierpaolo Mastroiacovo, Italy (Director, International Clearinghouse for Birth Defects); Moshe Hod, Israel (European Association of Perinatal Medicine); Yves Ville, France (International Society of Ultrasound in Obstetrics and Gynecology); Luis Cabero, Spain (Chair, FIGO Committee for Capacity Building in Education and Training); Claudia Hanson, UK and Tanzania (FIGO Safe Motherhood and Newborn Health Committee); Joe Leigh Simpson, USA (Vice President, March of Dimes).

a false-positive rate 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 thickness, fetal heart rate, and maternal serum free β -hCG and PAPP-A. The combined risk test has a detection rate of 90% for trisomy 21 and 95% for trisomies 18 and 13, with a false-positive rate 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 detection rate is increased to more than 95% and the false-positive rate decreased to less than 3%.
4. Screening by analysis of cfDNA in maternal blood has a detection rate of 99% for trisomy 21, 97% for trisomy 18, and 92% for trisomy 13, with a total false-positive rate 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 of gestation. In this case, we recommend the strategy below:
 - Combined test risk over 1 in 100: patients can be offered the options of cfDNA testing or invasive testing.
 - Combined test risk between 1 in 101 and 1 in 2500: patients can be offered the option of cfDNA testing.
 - Combined test risk lower than 1 in 2500: 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.

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 populations worldwide, especially in low- and middle-income countries. Each year, more than 4500 pregnancies in the European Union are affected by NTD. In the United Kingdom and Ireland, the prevalence of NTD declined from 4.5 per 1000 births in 1980 to 1.5 per 1000 in the 1990s. In contrast, in the rest of Europe the prevalence during the 1980s and thereafter remained close to 1 per 1000 births. In the USA, the incidence ranges from 1.4 to 1.6 per 1000 live births and 0.8 per 1000 births in Canada. In Latin America, the prevalence was about 5 cases per 1000 births in the northeastern and south region of Brazil, while in the southeast, the prevalence was 1 per 1000 births. In Mexico, the current prevalence is about 1 in 1000 births.

Evidence supports the hypothesis for the relationship between folate deficiency and NTD, including: (1) a randomized controlled trial for the prevention of primary occurrence or recurrence has confirmed that periconceptional folic acid supplementation reduces the rate of NTD, with a reduction rate of 72%; (2) folic acid antagonists (methotrexate, dihydrofolate reductase inhibitors, and others) increase the risk for NTD; and (3) the concentration of folate in red blood cells is lower in women who give birth to children with NTD.

Hence, folic acid supplementation is of great benefit, especially in low-resource country settings for several reasons. Firstly, the prevalence of NTD in low-resource countries is very high compared with the industrialized world. Secondly, folic acid supplements are readily available and affordable. Since iron supplementation is almost universally recommended in pregnancy, especially in low-resource country reproductive health programs, it would be convenient to combine the two interventions. Nevertheless, the keystone is pre-pregnancy administration of

synthetic folic acid supplement, which may not be easy in public health programs geared principally toward pregnant women.

FIGO recommends the following (see Table 1):

1. All women who plan to become pregnant or all women of child-bearing age with no contraceptive method and who do not present risk factors for NTD should utilize 400 μ g (0.4 mg) of synthetic folic acid, beginning at least 30 days before conception and continue daily supplements throughout the first trimester of pregnancy.
2. All women of reproductive age 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 optimal birth control.
3. Healthcare 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) folic acid supplementation of 400 μ g (0.4 mg) can be taken for years, without any known adverse 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 NTD.
4. Women who have risk factors for NTD should be advised that synthetic folic acid supplementation at a dose of 4000 μ g per day (4.0 mg) is recommended. It should start at least 30 days before the conception and continue 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 affected by NTD,
 - (d) prepregnancy diabetes,
 - (e) epilepsy treatment with valproic acid or carbamazepine,
 - (f) use of folate antagonists (methotrexate, sulfonamides, etc.).

Table 1

Summary of the FIGO recommendations regarding the administration of folic acid to prevent neural tube defects.

Population	Women who plan to become pregnant or are of childbearing age with no contraceptive method.
Recommendation	Daily supplementation of synthetic folic acid at a dose of 400 μ g.
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 ^a	High-risk factors include: <ul style="list-style-type: none"> • NTD-affected previous pregnancy • Partner affected by spina bifida • First-degree relative affected by NTD • Use of anticonvulsants • Pregestational diabetes • Obesity (BMI >35) • Use of folate antagonists (methotrexate, sulfonamides, etc.) • Malabsorption syndromes (including pregnant women with a history of surgery for obesity).
Recommendations from other associations	The American College of Obstetricians and Gynecologists, the American Academy of Family Physicians, the American Academy of Pediatrics, the National Institute for Health and Clinical Excellence (NICE) Guidance, and many other organizations have similar recommendations.

^a Women in the high-risk group should be instructed to use a daily dose of 4000 μ g (4 mg) for the same time recommended above.

- (g) malabsorption syndrome,
 - (h) obesity (body mass index >35; calculated as weight in kilograms divided by height in meters squared),
6. Finally, FIGO encourages the efforts of public agencies worldwide toward the development of more comprehensive programs to fortify food with synthetic folic acid and more vigilance in monitoring these programs.

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

At least 15 million babies worldwide are born preterm 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 high- and low-resource 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). Randomized 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.

FIGO recommends the following (see Table 2):

1. Sonographic cervical length measurement should be performed in all pregnant patients at 19–23 6/7 weeks of gestation using transvaginal

Table 2

FIGO 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	Transvaginal 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 micronized 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.

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 (90 mg vaginal gel or 200 mg 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, other devices may be used as a screening tool to measure objectively and reliably the cervical length.