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FIGO COMMITTEE REPORT

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Good clinical practice advice: Prediction of preterm labor and preterm premature rupture of membranes☆

FIGO Working Group on Good Clinical Practice in Maternal–Fetal Medicine*,[a]

*Correspondence: Gian Carlo Di Renzo, Department of Obstetrics and Gynecology, University of Perugia, Santa Maria della Misericordia University Hospital, Perugia, Italy. Email: giancarlo.direnzo@unipg.it

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[a]Working Group members and expert contributors are listed at the end of the paper.

PREMISE

Preterm birth (PTB) represents the main cause of death among newborns and the second cause, after pneumonia, during the first 5 years of live. Prediction of PTB and the associated preterm premature rupture of membranes (P-PROM) is actually based on the detection of risk factors and specific markers. Prediction of these events is important to enable women to be moved to a higher level center for safe confinement because nursery/neonatal intensive care is of utmost importance for the preterm neonate.

PTB is difficult to predict. At present there are no rigid and absolute standard parameters for its prediction, but there has been considerable interest in means of identifying women at risk of delivering prematurely by clinical symptoms and signs, biochemical markers, and cervical length by digital examination and/or ultrasound scan. To achieve this goal, a risk scoring system, biochemical markers derived from different body fluids (cervicovaginal fluid, blood, urine, saliva, amniotic fluid), tissues, and ultrasound parameters such as cervical length have been proposed.

ETIOPHATOGENESIS OF PTB AND P-PROM

About 80% of all preterm infants are live born singleton. Most of these deliveries are spontaneous, due to onset of contractions or to spontaneous P-PROM. Conversely, iatrogenic preterm deliveries are due to the physician's (usually with maternal/family consent) decision to induce labor for maternal and/or fetal medical reasons (severe fetal growth restriction, severe preeclampsia, etc.). However, since the terminology varies, it is crucial to use clear definitions in all circumstances in which the different phenotypical terms are used.[1]

Better described as a syndrome, PTB is the clinical manifestation of multiple and widely divergent antecedent conditions. The main etiology of spontaneous PTB is possibly ascending infection from the lower genital tract up in the sterile uterus invading the decidua, chorioamniotic membranes, amniotic fluid and, in some cases, also the fetus. Infection is responsible for an inflammatory reaction that triggers myometrial contractions, preterm premature rupture of the membranes, and cervical ripening (through several mediators), leading to PTB.[2–5] Several investigations have shown that the amount of bacteria present in the amniotic fluid is correlated to the level of intrauterine inflammation.[6–8] Recently, "sterile" intrauterine inflammation has been described, although it seems to be very uncommon in women with P-PROM.[9]

Several population-based and register-based studies have sought to create risk-based approaches to predict PTB, but success has been limited.[10,11] The main risk factors for PTB are history of previous preterm delivery and multiple pregnancy. Many maternal behaviors influence the risk of PTB, such as tobacco use, alcohol, and illicit drug abuse. Other factors are those related to nutritional habits, such as high intake of sugar-sweetened drinks[12] and modern Western diet,[13,14] which increases the risk of PTB, whereas other nutritional factors are associated with a decreased risk, such as intake of fish liver oil, probiotic milk, garlic, and other leek products. Other factors related to an increased risk of PTB are inadequate maternal body mass index (obesity and underweight), unemployment, chronic stress, catastrophic event, life events, and physical inactivity. Several other sociodemographic and community factors contribute to PTB risk, including low or high maternal age, material status, race, and ethnicity. Many maternal medical conditions also increase the risk of PTB: different types of diabetes, immunological diseases, rheumatologic conditions, and heart diseases.[15]

RATIONALE BEHIND SCREENING FOR PTB AND P-PROM

Although understanding of human labor and the causes of PTB have advanced over the past few years, the ability to accurately predict

when preterm labor or preterm premature rupture of membranes will occur has remains elusive. As a consequence, there has been development of targeted preventive therapies directed at specific at-risk subpopulations has been. Before undertaking any therapeutic decision, careful identification of women at risk for preterm labor and delivery with P-PROM is needed, so as to detect manageable conditions and fetal and/or maternal contraindications.

Several methods have been developed to identify both asymptomatic and symptomatic women at risk for PTB. It is imperative for clinicians to have a high level of suspicion when patients report symptoms such pelvic pain, back pain, menstrual-like cramps, and vaginal discharge, and in the presence of previous history for preterm birth. In most countries the identification of preterm labor is still based only on clinical data; a correct diagnosis is therefore very important to avoid unnecessary hospitalization, potentially harmful interventions, and waste of resources.[16] Current tests for the prediction of spontaneous preterm labor can be divided into three general categories: assessment of risk factors assessment, ultrasound measurement of cervical length, and biochemical markers. It should be emphasized that significant associations with labor may not necessarily translate into clinical predictive utility.

PREDICTION OF PTB IN SYMPTOMATIC WOMEN WITH INTACT MEMBRANES

Prediction involves the identification of women at risk for preterm delivery within a relatively short time interval (usually within 48 hours, 7–14 days). A test with high negative predictive value (NPV) and a high positive predictive value (PPV) would offer the greatest result.[17] The already proposed predictors have usually demonstrated a low PPV and a good NPV, and therefore are still not ideal for identifying all patients at risk. Transvaginal ultrasound measurement of cervical length (and detection of some biomarkers in cervical–vaginal secretions, including fetal fibronectin [fFN], placental alpha macroglobulin-1 [PAMG-1], and phosphorylated insulin-like growth factor binding protein 1 [phIGFBP-1]) currently represent the most important available tests for the prediction of PTB, both in symptomatic and asymptomatic women. Cervicometry can be applied as screening and has been proposed for universal screening in singleton gestations, without a previous preterm birth, in order to identify asymptomatic cases. It is recommended that cervicometry be performed in the second trimester at 18–23 weeks of gestation. The finding of a cervical length of less than 25 mm is associated with an increased risk of subsequent PTB with a sensitivity between 30% and 60%.[16]

On the basis of some known risk factors and pathways of preterm birth, several biomarkers have been tested to see if they can predict spontaneous preterm birth. The utility of biomarker testing in combination with cervical length measurement using transvaginal ultrasound has been examined to improve the clinical ability to diagnose preterm labor and predict imminent spontaneous PTB, especially in symptomatic women.[18,19] The PPV of most biomarker test results or a short cervix alone are poor, and it has been recommended that neither should be used exclusively to direct management in the setting of acute symptoms.[20,21]

fFN is an isoform of fibronectin with a unique IIICS region, and a component of the extracellular matrix of the membranes making up the amniotic sac, confined to the interface between the maternal and fetal units. fFN is found in amniotic fluid, placental tissue, and the extracellular component of the decidua basalis adjacent to the placental intervillous space. The test is available in two forms: qualitative and quantitative fFN detection. In qualitative detection, an fFN level of 50 ng/mL is a positive result and a level of less than 50 ng/mL is a negative result.[16] In line with several previous systematic reviews, a recent systematic review suggested that the sensitivity of qualitative fFN testing may be highest for prediction of PTB within 7–10 days of testing.[22] Most recently a quantitative bedside fetal fibronectin test has been developed, and while one study has demonstrated enhanced clinical utility compared with the traditional qualitative test, another has concluded that quantitative fFN testing does not improve the prediction of PTB within 7 days compared with qualitative fFN testing in combination with cervical length measurement in terms of reclassification from high to low (<5%) risk.[23] A threshold of 10 ng/mL has high sensitivity and NPV to determine those women unlikely to deliver prematurely.

phIGFBP-1 is produced by the placental decidual cells and thought to be released into the cervical vaginal fluid after tissue damage to the choriodecidual interface.[24] A qualitative test, either positive or negative, is measured from a vaginal swab taken with a speculum between 22 and 36 weeks of gestation. An immunochromatography-based dipstick test is used to obtain the result within 5 minutes. The test reported pooled sensitivity and specificity in some studies.[24] Among women with a singleton gestation and 30 mm cervical length, a positive cervical phIGFBP-1 test (summary likelihood ratio of 5.5) increased the pretest probability of delivery within 7 days of testing from 17.8% to 54.4%, whereas a negative test result (summary likelihood ratio of 0.3) decreased the risk to 6.1%. One advantage is this test maybe less prone to influence with sexual intercourse, known to increase the false positive rate with fFN.[25,26]

PAMG-1 is another glycoprotein synthesized by the decidua. It is present in the amniotic fluid in high concentrations, but few data are available on the cervicovaginal fluid content.[27] A vaginal swab can be inserted directly into the vagina, removing the need for a speculum in patients between 20 and 37 weeks of gestation. An immunoassay bedside dipstick test is used to obtain the result within 5 min. Lee et al. explained the presence of PAMG-1 in cases of threatened preterm labor by a transudation of PAMG-1 through chorioamniotic pores in fetal membranes during uterine contractions, or by the degradation of extracellular matrix of fetal membranes due to inflammatory process of labor and/or infection. The clinical value of a positive PAMG-1 test in patients presenting with symptoms and signs of PTB without membranes rupture was investigated and the results demonstrated that PAMG-1 detection was highly predictive of delivery of these patients within 48 hours, 7 days, and 14 days, providing both a high NPV and PPV, which was found to be higher than fFN testing.[27] Several additional early studies have corroborated these findings.[28,29]

Authors also compared fFN and PAMG-1 for detection of PTB within 7 days: they reported sensitivities of 80% and 50%, specificities of 95% and 72%, NPVs of 96%, and 87%, and PPVs of 76% and 29%, for PAMG-1 and fFN, respectively.[30] Another study reported that the PAMG-1 test predicted spontaneous PTB within 14 days, with 100% sensitivity, 98% specificity, 75% PPV, and 100% NPV,[31] and others confirmed similar results.[32] Neither fFN nor PAMG-1 should be used in case of vaginal bleeding, due to their presence also in maternal blood.

A recent study assessed the efficacy of PAMG-1 in cervicovaginal secretions collected immediately after transvaginal ultrasound of women with symptoms and signs of preterm labor, intact membranes, and a cervical length of 15–30 mm.[33] For PTB prediction risk within 7 days of testing, sensitivity is 100% and specificity is 94%. PPV is 77% and NPV is 100%. For delivery prediction at less than 34 weeks of gestation, sensitivity decreased from 100% to 67% and specificity from 94% to 89%, PPV is 55%, and NPV 93%. The PAMG-1 test demonstrated high efficacy in identifying women at risk of imminent preterm labor within 7 days of testing, despite being performed immediately after transvaginal ultrasound. High NPV can prevent improper admission and therapies for mother and fetus.

Another study compared the predictive value of PAMG-1 and phIGFBP-1 in a prospective analysis.[34] In patients with history of preterm delivery and cervical length of 15–30 mm, PAMG-1 showed a higher predictive value in identifying those likely to deliver within 7 days of testing.

Some therapeutic interventions are available for the prevention of spontaneous PTB and improvement of maternal/fetal outcomes, such as use of progesterone and cervical pessary, tocolytic therapy, antenatal corticosteroids, and magnesium sulphate administration. Despite advances in selection of eligible women for such therapeutic strategies, the efficacy of cervical length and fetal fibronectin levels (or PAMG-1, phIGFBP-1) are still limited.

In the last few years, interest in the prediction strategies of preterm labor/P-PROM has increased and several studies have been published. Lee et al. investigated whether the level of vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and soluble VEGF receptor-1 (sFlt-1) in mid trimester amniotic fluid of preterm birth have different values compared with term delivery.[35] This study reported that it is feasible to measure the VEGF, PlGF and sFlt-1 concentrations in mid-trimester amniotic fluid for the prediction of spontaneous preterm birth for asymptomatic women. These angiogenic parameters can be useful and strong biomarkers to distinguish high-risk patients, discriminate the expected preterm birth, and provide the understandable key for the complex mechanism of preterm labor.[35] Recently, use of metabolomics for the identification and validation of clinical biomarkers for preterm delivery was proposed: the Preterm SAMBA study associates metabolomics technologies to identify clinical and metabolite predictors for preterm birth. These innovative and unbiased techniques might be a strategic key to advance spontaneous preterm birth prediction.[36]

It is also very interesting that the fetal adrenal zone enlargement and corrected fetal adrenal gland volume have been studied in preterm birth prediction.[37] Patients were categorized as preterm (women with signs and symptoms of preterm labor) and term groups. Both groups underwent transabdominal ultrasonography in which cervical length, cervical shear wave speed (dynamic elastography), and fetal adrenal gland parameters were measured. The findings showed a strong correlation between dynamic elastrography and fetal adrenal biometry as objective predictors of preterm birth.

There are also new developments for early prediction in the first trimester of pregnancy. Kansu-Celik et al. have been proposed an early marker for prediction of preterm labor/P-PROM: first-trimester maternal serum advanced glycation end products (AGEs) levels were significantly higher in cases complicated with preterm labor/P-PROM and might be useful marker.[38] Winger et al. investigated the capacity of first trimester peripheral blood mononuclear cell (PBMC) microRNA to determine risk of spontaneous preterm birth among pregnant women: quantification of PBMC microRNA may provide a good sensitive and specific prediction of PTB, but larger studies are needed for confirmation.[39]

Finally, a recent study focused on the potential role of maternal serum ferritin in prediction of preterm labor, which was found to be elevated in women who delivered preterm.[40] This study showed that serum ferritin 31 ng/mL is the optimal cut-off between preterm and full-term women. These findings for clinical practice and/or further research could be proposed as a potential helpful marker to predict preterm labor.

PREDICTION OF P-PROM AND P-PROM/ PRETERM DELIVERY LATENCY

P-PROM is the largest identifiable cause of preterm birth. There is currently no optimal screening test for P-PROM in low-risk asymptomatic patients. Accurate P-PROM diagnosis is essential for patient management. Traditional approaches to diagnosis of rupture of fetal membranes are now powered by scientific progress: biomarkers and the search for an accurate test is in dynamic evolution. P-PROM occurs in about 3% of all pregnancies and in 30% of all preterm births. It is estimated that 20%–25% of pregnancies present suspicion of P-PROM; of these, 40% have no obvious leakage of fluid from the cervical os and 47% clinicians are uncertain about the diagnosis based only on physical examination.

In a woman reporting symptoms suggestive of P-PROM, a speculum examination could be used to look for pooling of amniotic fluid and, if pooling of amniotic fluid is observed, no diagnostic test would be performed. If no pooling of amniotic fluid is observed, a phIGFBP-1 or PAMG-1 test of cervico-vaginal fluid could be performed. If the results of phIGFBP-1 or PAMG-1 are positive, the test results alone should not be used to decide the therapeutic strategy, and maternal clinical status, medical and pregnancy history, and gestational age should also be accounted for. The ideal biomarker characteristics are very low or non-existent concentration in background cervico-vaginal discharge when fetal membranes are intact, threshold close to maximum background concentration, and very high concentrations in amniotic fluid. fFN and phIGFBP-1 were initially used in the 1990s

as premature rupture membranes markers, and only later were they reinvented as preterm labor biomarkers. Several comparative studies arrived at the same conclusion that PAMG-1 is superior to phIGFBP-1 for diagnosis of rupture of fetal membranes.

Ramsauer et al. compared the performance of tests based on the detection of insulin-like growth factor binding protein 1 (IGFBP-1) and PAMG-1 in diagnosis of rupture of fetal membranes across different patient populations.[41] Compared with its performance in women with known membrane status, the accuracy of the IGFBP-1 test decreases significantly when used in patients whose membrane status is unknown, and PAMG-1 has higher accuracy than phIGFBP-1. A few years later, Ramsauer et al. deepened their research by studying the influence of blood on the diagnostic accuracy of PAMG-1 and phIGFBP-1 tests in rupture of fetal membranes.[42] The presence of blood may lead to false positive results with biochemical markers. This study observed that the PAMG-1 detecting test was significantly less susceptible to interference by blood than the IGFBP-1 detecting test in all quality parameters evaluated (sensitivity was 97.8% vs 91.0%, specificity was 91.5% vs 75.0%, PPV was 94.6% vs 83.5%, and NPV was 96.4% vs 85.7%).

Nunes et al. reviewed the literature on fetal membrane thickness and its potentially use for the prediction of P-PROM. The area of fetal membrane imaging to predict the risk of preterm birth has exciting potential. Emerging technologies such as shear wave elastography, optical coherence tomography and fusion MRI imaging hold the promise of improved examination of the fetal membranes. Along with advances in ultrasound technology, future studies may be able to identify characteristics of the fetal membranes that are predictive of P-PROM.[43]

Mehra et al. demonstrated that a shorter transvaginal cervical length and an amniotic fluid index 5 cm or less predicted delivery within 7 days in women presenting with P-PROM. The combination of an amniotic fluid index greater than 5 cm and transvaginal cervical length greater than 2 cm greatly improved the potential to remain undelivered at 7 days following cervical length assessment. These findings may be helpful for counselling and optimization of maternal and neonatal care in women with P-PROM.[44]

A recent study proposed maternal C-reactive protein (CRP) and oxidative stress markers as predictors of delivery latency in women experiencing P-PROM. CRP, lipid peroxide, and oxygen radical absorbance capacity levels seem to be useful in predicting delivery within 3 days after P-PROM.[45] Gezer et al. identified urea and creatinine levels in cervico-vaginal fluid as potential predictors of P-PROM and P-PROM/preterm delivery interval. In multivariate logistic regression analysis, vaginal fluid urea and creatinine levels were found to be significant predictors of P-PROM (both $P<0.001$) and delivery within 48 hours after P-PROM ($P=0.012$ and $P=0.017$, respectively).[46]

Kemin et al. evaluated the diagnostic value of procalcitonin and CRP for the prediction of suclinical intrauterine infection in patients with P-PROM. Both parameters are good predictive and diagnostic indicators for PROM associated with chorioamnionitis, and procalcitonin is more suitable for pregnant women at $28–33^{+6}$ weeks.[47] Moreover, amniotic fluid interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) seem to be good predictors for fetal inflammatory response syndrome and may improve the clinical management of patients with P-PROM. The non-invasive technique of sampling amniotic fluid from vaginal secretions facilitates daily measurements and bedside assessment of cytokines, and is in this respect preferable to invasive amniocentesis.[48]

Another model comprising maternal serum levels of IL-6 associated with maternal characteristics proved to be a good non-invasive predictor infection in pregnancies complicated with P-PROM.[49] Several maternal serum markers were studied for the prediction of histological chorioamnionitis (HCA) after P-PROM. A blood sample was obtained before delivery and analyzed for CRP, intercellular adhesion molecule-1, IL-6, IL-8, matrix-metalloproteinase (MMP) 8 and 9, triggering receptor on myeloid cells, and human neutrophile peptides. HCA was determined by histological examination distinguishing maternal from fetal inflammatory response. CRP was the best maternal marker for prediction of HCA in women with P-PROM.[50]

It is also hypothesized that presepsin (another inflammatory marker released from monocytes and macrophages as an acute reaction to infection) may be useful in pregnancies with P-PROM for diagnostic and prognostic purposes. The striking fluctuations in presepsin level after the diagnosis of P-PROM can be used to predict subclinical chorioamnionitis and determine the optimal timing of delivery before the clinical signs of chorioamnionitis are established.[51] Other inflammatory markers have been evaluated for their ability to predict and diagnose rupture of fetal membranes at early stage. Toprak et al. investigated the relationship between the platelet-to-lymphocyte ratio and P-PROM. The platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios were both significantly higher in the P-PROM group ($P<0.001$). The ability of the platelet-to-lymphocyte ratio to diagnose preterm premature rupture of membranes was evaluated using a receiver operating characteristic curve. The sensitivity and specificity of the platelet-to-lymphocyte ratio was 57.8% and 73.7%, respectively, at a threshold of greater than 117.14 ($P<0.001$). As such, it might be a cost effective, easy to use, and practical marker for the early diagnosis of P-PROM, which can help to determine the appropriate management.[52]

The maternal serum and vaginal fluid of soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble intercellular adhesion molecular (sICAM-1) levels could be used as biochemical markers supporting the P-PROM diagnosis because of the increase in both maternal serum and vaginal fluid sVCAM-1 and sICAM-1 levels in pregnant women with preterm rupture of membranes.[53]

Wang et al. recently examined the proteome profile of amniotic fluid and maternal plasma for their diagnostic and prognostic value in P-PROM. The proteome profiles of amniotic fluid and maternal plasma were examined via liquid chromatography coupled with tandem mass spectrometry-based proteomic techniques. 12 of 540 unique proteins were chosen for further detection. Placental protein 14 was observed to have excellent diagnostic accuracy for P-PROM, with a respective sensitivity and specificity of 100% and 87.5% when the cut off value was 0.008 μg/mL.[54]

High-mobility group box 1 (HMGB1) is a novel identified inflammatory cytokine, and the HMGB1— receptor for advanced glycation end

products (RAGE) signaling pathway has been associated with many pathophysiological processes, including P-PROM. HMGB1 nuclear-cytoplasmic translocation in P-PROM placenta may lead to the binding of HMGB1 to RAGE, resulting in provoking NF-κBp65 activity and the consequent release of MMP-9 and MMP-2, all of which contribute to the P-PROM.[55]

Feng et al. observed that prothrombin can be directly produced by fetal membrane, amnion, chorion, and decidua cells. Furthermore, prothrombin production can be stimulated by *Ureaplasma parvum* exposure in fetal membranes. These findings represent a potential novel underlying mechanism of *U. parvum*-induced P-PROM and the potential use of prothrombin as a predictor of this unfavorable event.[56]

Timing of delivery is often unknown; approximately half of women who are admitted to hospital with threatened preterm birth remain undelivered after 7 days.[57,58] Several other studies have reported increased odds ratios and/or predictive efficiency for preterm birth when two or more biomarkers (sometimes derived from different tissues) are combined compared to single biomarkers alone.[59–61]

In conclusion, the present short review shows that clinical research on the predictive strategies of P-PROM and preterm labor is very active and in dynamic evolution. New and interesting parameters have been proposed in recent years to improve the prediction of these events as much as possible, to make rational and safe use of the available therapeutic strategies, to improve the outcomes of newborns (prevention of related morbidities) in the short and long term, and to optimize the use of resources.

FIGO recommends the following for prediction of PTB:

1. Proper identification of symptomatic patients in true PTB is essential.
2. Take into consideration new risk factors (age, medically assisted technologies for pregnancy, fetal male sex, psychosocial stress, previous cesarean section, etc.).
3. Before undertaking any therapeutic strategy, careful identification of women at risk for PTB and delivery is needed, so as to detect manageable conditions and fetal and/or maternal contraindications.
4. Use of cervical length measurements and of biochemical markers, especially if combined, improves identification of symptomatic patients at risk for imminent spontaneous PTB as compared with the clinical symptoms alone (i.e. vaginal bleeding, contraction frequency/duration, cervical dilation, etc.).
5. Of the available biochemical tests, that based on fetal fibronectin (fFN) has been the best characterized. However, the value of this test, like that of phosphorylated insulin-like growth factor protein-1 (phIGFBP-1) and cervical length measurement alone, may be limited only to their negative predictive value (NPV), given its poor positive predictive value (PPV).
6. While a cervical length of less than 1.5 cm and more than 3.0 cm has high predictive value to identify patients at risk or to exclude the risk, most patients presenting with symptoms of PTB have a cervical length within these limits. Thus, we recommend the use of transvaginal ultrasound to measure cervical length in patients presenting with symptoms of PTB in order to assess their risk of imminent PTB.
7. In patients in whom the CL is between 1.5 cm and 3.0 cm, it may be recommended for a biomarker test with the highest combination of NPV and PPV to be run shortly after a vaginal examination. According to recent literature, this test seems to be that based on placental alpha-microglobulin-1 (PAMG-1; PartoSure).
8. Use of steroids should be reduced by adequate PTB risk assessment and by avoidance of early elective cesarean section. Cervical length measurement, in combination with PAMG-1 testing can help to determine which women are at low risk of delivery within 7 days, and perhaps allow more judicious use of antenatal treatments.

FIGO recommends the following for diagnosis of preterm premature rupture of membranes (P-PROM):

9. P-PROM is one of the leading causes of PTB, and its proper identification is essential.
10. Biochemical markers are better than the traditional methods, as they are specific to proteins found in amniotic fluid.
11. The rapid strip test based on PAMG-1 seems to be a more sensitive bedside test than other tests.

FIGO WORKING GROUP ON GOOD CLINICAL PRACTICE IN MATERNAL–FETAL MEDICINE (2015-2018)

Gian Carlo Di Renzo, Italy (Chair); Eduardo Fonseca, Brazil; Eduardo Gratacos, Spain; Sonia Hassan, USA; Mark Kurtser, Russia; Fergal Malone, Ireland; Shilpa Nambiar, Malaysia; Kypros Nicolaides, UK; Nancy Sierra, Mexico; Huixia Yang, China (members). Carlos Fuchtner, Bolivia (FIGO President Elect, Ex Officio); Vincenzo Berghella, USA (Society for Maternal–Fetal Medicine); Ernesto Castelazo Morales, Mexico (FIGO Committee for Capacity Building in Education and Training); Mark Hanson, UK (FIGO Working Group on Adolescent, Preconception and Maternal Nutrition); Moshe Hod, Israel (Committee on Pregnancy and NCD; Working Group on Hyperglycemia in Pregnancy); Yves Ville, France (International Society of Ultrasound in Obstetrics and Gynecology); Gerard Visser, Netherlands (FIGO Committee for Safe Motherhood and Newborn Health); Joe Leigh Simpson, USA (March of Dimes).

EXPERT CONTRIBUTORS

Abdallah Adra (Department of Obstetrics and Gynecology, American University of Beirut Medical Center, Lebanon); Roza Bataeva (Fetal Medicine Centre, Russian Medical Academy of Advanced Studies, Moscow, Russia); Luis Cabero Roura (Autonomous University of Barcelona, Hospital Materno-infantil Valle Hebron, Barcelona,

Spain); Ramen H. Chmait (Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Keck School of Medicine, University of Southern California, USA); Yvonne Cheng (Department of Obstetrics and Gynaecology, Chinese University of Hong Kong); Irene Giardina (Centre of Perinatal and Reproductive Medicine, University of Perugia, Italy); Jon Hyett (Department of Women and Babies, Royal Prince Alfred Hospital, Australia); Asma Khalil (Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St. George's University Hospitals NHS Foundation Trust, London, UK); Narendra Malhotra (Global Rainbow Healthcare, India); Pierpaolo Mastroiacovo (Alessandra Lisis International Centre on Birth Defects and Prematurity, International Clearinghouse for Birth Defects Surveillance and Research, Rome, Italy); John Morrison (Department of Obstetrics & Gynaecology, National University of Ireland); Amala Nazareth (Emirates Medical Association Ob Gyn, United Arab Emirates); Liona Chiu Yee Poon (Department of Obstetrics and Gynaecology, Chinese University of Hong Kong); Chittaranjan N. Purandare (International Federation of Gynecology and Obstetrics [FIGO], St. Elizabeth Hospital, Walkeshwar and BSES Hospital Mumbai, India); Ruben Quintero (Plantation General Hospital and Wellington Regional Medical Center, Coral Gables, Florida, USA); Waldo Sepulveda (Maternal–Fetal Diagnostic Center, Santiago, Chile); Valentina Tosto (Centre of Perinatal and Reproductive Medicine, University of Perugia, Italy).

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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