EDITORIAL

FIGO good practice recommendations for reducing preterm birth and improving child outcomes

In this issue of International Journal of Gynecology & Obstetrics, the FIGO (International Federation of Gynecology and Obstetrics) Working Group for Preterm Birth provides nine FIGO good practice recommendations. The project started and developed from the FIGO Working Group meetings in London, December 2019, and at the Society of Maternal Fetal Medicine meeting in Dallas, February 2020. The idea was to try to highlight the most important low-hanging fruits for reducing preterm births and improving child outcomes after preterm birth.

Each document was drafted initially by selected Working Group members and discussed on multiple occasions. Consensus was reached as to the breadth and depth necessary for healthcare providers and FIGO member societies. Materials used to construct the recommendations include those from WHO, governmental healthcare agencies, professional societies, and global collaborative networks (e.g., Cochrane). The Working Group naturally sought randomized clinical trials in high-impact peer-reviewed journals, and robust analysis. The latter included literature based on aggregate data, but ideally individual patient data. When consensus was reached, Working Group recommendations were in alignment with FIGO policy. Documents were stratified into three categories with recommendations provided: population-based registries 1–3; prevention by maternal treatment 4–6; and fetal treatment imminent to delivery. 7–9

1 | POPULATION-BASED PREVENTION OF PRETERM BIRTH

The FIGO Working Group for Preterm Birth recognizes that reducing preterm birth at the population level requires the ability to track changes in the general population to determine frequency and causes known to be associated with preterm birth. Useful data must be accessible, accurate, and timely. Three FIGO Working Group recommendations address population-based methods for preterm birth prevention.1–3

Frøen, Bianchi, Moller, and Jacobsson1 speak for the Working Group in advocating not only universal healthcare coverage but also sustained access to quantitative preventive strategies to fulfill the global Sustainable Development Goals for women’s, children’s and adolescents’ health. The authors recommend strengthening health information systems to ensure timely access to actionable high-quality data. This good practice recommendations document states that “every individual counts and should be counted individually”, in particular mother-child dyads, from pre-conception to pediatrics, and later in life. A second recommendation calls for strengthening investments in digital registries, enabling integration with reproductive, maternal, newborn, and child health services adhering to targeted WHO recommendations.

In a second good practice recommendations document, Valencia, Mol, and Jacobsson2 address the 30%–35% of preterm deliveries believed to be iatrogenic-related. The Working Group recommends efforts to identify the contribution of iatrogenic preterm delivery to the overall preterm birth rate and encourages health authorities to establish preventive measures accordingly. For example, achieving a reduction in preterm deliveries is also possible by reducing cesarean deliveries, given the later risk of related pregnancy complications (e.g., uterine rupture or placenta accreta). The document also recommends avoiding multiple embryo transfers in assisted reproductive technologies (ART). Once considered necessary in order to achieve an acceptable pregnancy rate, there is less need at present for multiple embryo transfer to achieve suitable pregnancy rates. Single embryo transfer (SET) is now recommended: 50%–60% pregnancy rates can be achieved with SET accompanied by ancillary diagnostic tests. A third recommendation calls for access to adequate pregnancy dating and clinical practice guidelines that minimize nonmedically-indicated preterm delivery.

The topic of the third FIGO good practice recommendations document in the population category has already been alluded to—namely, the reduction of preterm births by SET in ART. Mol, Jacobsson, Grobman, and Moley3 acknowledge that ART has enabled infertile couples to achieve pregnancy. SET is, as previously noted,2 recommended as the best approach to ensure a healthy neonate. Nevertheless, even a singleton ART pregnancy carries more complications than a singleton pregnancy after spontaneous

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conception; FIGO recommends that couples and individuals should be advised of this. Minimal embryo manipulation during cell culture is also recommended. Attention is called to the increased risks of birth defects (odds ratio 1.3), and increased rate of pregnancy complications in ART. The extent to which these increases reflect the underlying reason for infertility will require investigation and communication with patients.

2 | MATERNAL TREATMENT TO PROLONG GESTATION

The second set of good practice recommendations deals with therapeutically extending gestational length to decrease preterm birth rate. This strategic approach has existed for decades. One topical issue involves administration of a progestogen (vaginal progesterone or intramuscular 17-hydroxyprogesterone caproate [17-OHPC]). A surgical option is cervical cerclage, while a non-surgical option is insertion of a pessary.

Shennan, Suff, Simpson, Jacobsson, Mol, and Grobman speak for the Working Group in reviewing efficacy of progestogens in preventing preterm births. Current options include vaginal progesterone daily or 17-OHPC. A timely 2021 landmark individual patient data meta-analysis by the EPPPIC group encompassed 31 randomized clinical trials and 11,644 participants. Eligible women in these RCTs were considered by their providers to be at high risk of preterm birth, largely because of previous spontaneous preterm birth or because of a sonographic short cervix. Analyzing these and other data, the Working Group recommended offering either daily vaginal progesterone or weekly intramuscular 17-OHPC. EPPPIC showed reduction of preterm birth before 34 weeks of gestation. For vaginal progesterone the risk ratio (RR) was 0.78 (95% CI 0.68–0.90); for 17-OHPC the RR was 0.83 (95% CI 0.68–1.01). As expected, greatest absolute benefit occurred when prevalence in a subgroup was highest, for example in those with a shorter cervix. The Working Group did not recommend progestogens for asymptomatic women who lacked prior history of preterm birth or who lacked short cervical length, either in singleton or multiple pregnancies. No evidence was found for either neurological or developmental benefit or harm in babies whose mothers received progestogens.

Shennan, Story, Jacobsson, and Grobman prepared the good practice recommendations on cervical cerclage. Placing a surgical suture should logically impede preterm dilatation. Cohorts studied have not been universally restricted to women with prior preterm birth. Asymptomatic women having certain obstetrical or gynecological procedures are logically at increased susceptibility for cervical shortening. Ultrasound can identify women with cervical shortening despite no prior preterm births. Randomized control trials and requisite meta-analyses were reviewed. The Working Group consulted multicenter trials, one encompassing 1292 women in whom cerclage was performed during the first trimester. In those who had experienced three or more prior preterm births or second trimester losses, gestational length <33 weeks was 15% in the cerclage group versus 32% in the control group. Statistically significant benefit was not seen with only one or two prior preterm deliveries. The Working Group also recommended cerclage in the context of short cervical length (<25 mm) when accompanied by prior preterm birth or mid-trimester loss. Müllerian anomalies and gynecological procedures such as cervical conization have traditionally been considered to place pregnancies at increased risk of preterm birth. Still, the Working Group considered there to be no clear benefit of cerclage without prior preterm birth in women with short cervix or history of cervical surgery. Rather, the recommendation was for individualized treatment. The Working Group further stated that transabdominal cerclage can be considered in the context of a prior failed vaginal cerclage. Potential infectious morbidity to mother and baby must be taken into account.

The Working Group also assessed use of pessary to prevent preterm delivery. Despite ongoing randomized clinical trials, no recommendation can be given for routine pessary use. The two most robust RCTs arrived at disparate results. The recommendation against pessary use was similar for twin gestations, irrespective of cervical length. Failure to recommend pessary was based on the Working Group finding inconsistency among studies and failing to identify a specific group of individuals who would benefit from pessary placement.

3 | OBSTETRICAL MANAGEMENT IMMINENT TO DELIVERY OF NEONATE

The third category of approaches to reduce preterm birth involves obstetrical management imminent to preterm delivery. Speaking on behalf of the Working Group, Norman, Shennan, Jacobsson and Stock reviewed RCTs that encompassed 27 trials involving administration of betamethasone, dexamethasone or hydrocortisone; control arms received either no treatment or placebo. Significant benefit was seen in reduction of perinatal death, respiratory distress (RR 0.58, 95% CI 0.45–0.75), and necrotizing enterocolitis (0.50; 95% CI 0.32–0.97). The FIGO Working Group recommended that when active neonatal care was appropriate, prenatal corticosteroid should be administered to the mother between 24 + 0/7 and 34 + 0/7 weeks in a singleton pregnancy. This recommendation held also for multiple pregnancies. Administration of corticosteroids was not recommended routinely for women imminent for preterm birth between 34 + 0/7 to 36 + 6/7 weeks or for elective cesarean delivery at term.

Dosage recommendations were made: two intramuscular 12 mg doses of betamethasone acetate/phosphate 24 h apart, or two intramuscular 12 mg doses of dexamethasone 24 h apart. The Working Group reviewed inconsistencies between the ACT Cluster randomized clinical trial, which failed to reduce neonatal mortality, and the ACTION trial, which did show benefit, and clarified that prenatal corticosteroids should be also used in a low-resource setting.

An important recommendation is also that prenatal corticosteroids should not be given “just in case”, but reserved for women for
women with an imminent preterm birth delivery based on the woman's symptoms or an accurate predictive test.

Working Group authors Shennan, Suff, and Jacobsson addressed the value of administration of magnesium sulfate for fetal neuroprotection. This good practice recommendations document emphasizes that 25% of cerebral palsy cases occur before 34 weeks, implying correlation with preterm birth. The Working Group agreed with Cochrane reviews, concluding that cerebral palsy was reduced (RR 0.68; 95% CI 0.54–0.87) when MgSO4 was administered before 34 weeks. MgSO4 was recommended from viability to 30 weeks. If resources allow, MgSO4 can be considered from viability to 34 weeks, and should be administered within 24 h of delivery and as close to 4 h before delivery as possible. The recommended initial dose of MgSO4 is 4–6 g, followed by 1 g/h intravenous maintenance and preeclampsia screening. Bo Jacobbson is also Chair of the FIGO Working Group for Preterm Birth*

Bianchi, Jacobsson, and Mol authored the good practice recommendations for delayed umbilical cord clamping. A thorough rationale is provided. Improved neonatal hematologic indices and reduced hospital mortality have been shown when performed at various timelines (<34 weeks; <28 weeks). The Working Group concluded, however, that insufficient evidence exists to set a precise duration of delay, but current evidence supports not clamping the cord before 30 s for preterm births. Future trials could compare different lengths of delay. Until then, a period of 30 s to 3 min seems justified for term-born babies.

CONFLICTS OF INTEREST
Collated conflict of interest statements from all Working Group members and collaborators who contributed to the series of good practice recommendations documents are listed here.

Ana Bianchi reports no conflicts of interest. Andrew Shennan reports payment/honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Manipal India; support for attending meetings and/or travel from Hologic; leadership or fiduciary roles in the HTA Commissioning Board UK and Action on Pre-eclampsia charity. Ann-Beth Moller reports no conflicts of interest. Ben W. Mol reports an investigator grant from NHMRC; consultancy for ObsEva; and research funding from Guerbet, Ferring, and Merck KGaA. Bo Jacobsson reports research grants from Swedish Research Council, Norwegian Research Council, March of Dimes, Burroughs Wellcome Fund and the US National Institute of Health; clinical diagnostic trials on NIPT with Ariosa (completed), Natera (ongoing), Vanadis (completed) and Hologic (ongoing) with expenditures reimbursed per patient; clinical probiotic studies with product provided by FukoPharma (ongoing, no funding) and BioGaia (ongoing; also provided a research grant for the specific study); collaboration in IMPACT study where Roche, Perkin Elmer and Thermo Fisher provided reagents to PLGF analyses; coordination of scientific conferences and meetings with commercial partners as such as NNFM 2015, ESPBC 2016 and a Nordic educational meeting about NIPT and preeclampsia screening. Bo Jacobsson is also Chair of the FIGO Working Group for Preterm Birth and the European Association of Perinatal Medicine's special interest group of preterm delivery; steering group member of Genomic Medicine Sweden; chairs the Genomic Medicine Sweden complex diseases group; and is Swedish representative in the Nordic Society of Precision Medicine. Joe Leigh Simpson reports royalties from Springer and Elsevier; consulting fees from the Illumina Clinical Expert Panel 2020; payment or honoraria for lectures, presentations, speakers bureaus, or educational events from the 1st and 2nd International Congresses on the Future of Women's Health, and a speaker's bureau at ASRM 2019; participation on a data safety monitoring board or advisory board for the FDA DSMB; and leadership or fiduciary roles in IFFS and PGDIS. Catalina M. Valencia reports no conflicts of interest. J. Frederik Frøen reports no conflicts of interest. Jane Norman reports receipt of grants from government and charitable bodies for research into understanding the mechanism of term and preterm labour and understanding treatments; participation in a Data Safety and Monitoring Board for a study involving a preterm birth therapeutic agent for GlaxoSmithKline; and consultancy for Dilafor on drugs to alter labour progress. Joe Leigh Simpson reports royalties from Springer and Elsevier; consulting fees from the Illumina Clinical Expert Panel 2020; payment or honoraria for lectures, presentations, speakers bureaus, or educational events from the 1st and 2nd International Congresses on the Future of Women's Health, and a speaker's bureau at ASRM 2019; participation on a data safety monitoring board or advisory board for the FDA DSMB; and leadership or fiduciary roles in IFFS and PGDIS. Kelle Moley reports no conflicts of interest. Lisa Story reports receipt of equipment, materials, drugs, medical writing, gifts or other services from Clinical Innovations. Natalie Suff reports no conflicts of interest. Sarah J. Stock reports research funding from NIHR, Wellcome Trust, Chief Scientist Office Scotland, Tommy's, and Medical Research Council; participation on a Data Safety Monitoring Board or Advisory Board for NIHR-funded WILL trial and NIHR-funded Giant Panda; leadership or fiduciary roles for SANDS and RCOG Stillbirth Clinical Studies Group; and receipt of equipment, materials or drugs from Hologic, Medix Biochemica, and Parsogen Diagnostics. Stephen Mujanja reports no conflicts of interest. William Grobman reports no conflicts of interest.

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