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EDITORIAL

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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 Jacobsson[1] 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.[10] 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 Jacobsson[2] 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 Moley[3] 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

*The Members of the FIGO Working Group for Preterm Birth, 2018–2021 are listed at the end of the article.

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.[4–6] 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.[4] 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.[11] 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[5] 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.[12] 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.[6] Despite ongoing randomized clinical trials, no recommendation can be given for routine pessary use. The two most robust RCTs[13,14] 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.[7] 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) (15). 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,[15] which failed to reduce neonatal mortality, and the ACTION trial,[16] which did show benefit, and clarified that prenatal corticosteroid 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.[8] 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,[17] concluding that cerebral palsy was reduced (RR 0.68; 95% CI 0.54–0.87) when $MgSO_4$ was administered before 34 weeks. $MgSO_4$ was recommended from viability to 30 weeks. If resources allow, $MgSO_4$ 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 $MgSO_4$ is 4–6 g, followed by 1 g/h intravenous maintenance thereafter. Monitoring clinical signs is necessary at least every 4 h: pulse, blood pressure, respiratory rate, and deep tendon reflexes.

Bianchi, Jacobsson, and Mol authored the good practice recommendations for delayed umbilical cord clamping.[9] 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 Jacobbson 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 expendidures reimbused 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 Jacobbson 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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SPECIAL ARTICLE

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FIGO good practice recommendations on the importance of registry data for monitoring rates and health systems performance in prevention and management of preterm birth

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Abstract

FIGO calls for strengthening of health information systems for reproductive, maternal, newborn, and child health services, co-designed with users, to ensure the timely accessibility of actionable high-quality data for all stakeholders engaged in preventing and managing preterm birth consequences. FIGO calls for strengthening of investments and capacity for implementing digital registries and the continuity of reproductive, maternal, newborn, and child health services in line with WHO recommendations, and strengthening of the science of implementation and use of registries—from local quality improvement to big data exploration.

KEYWORDS
health systems strengthening, high-quality data, preterm birth, prevention, registry

1 | INTRODUCTION

Universal health care coverage, including financial risk protection, is one of the cornerstones of the Global Sustainable Development Goal (SDG) Framework[1] as well as the Global Strategy for Women's, Children's and Adolescents' Health (2016–2030).[2] However, the lack of effective strategies for preventing and managing preterm birth and its consequences is still of significant concern in many low- and middle-income countries (LMICs). Several LMICs struggle to ensure equitable access to use and quality of care even for primary health care for pregnant women and newborns. Despite the evidence of effective preventive strategies, such as antenatal care, many pregnant

* The Members of the FIGO Working Group for Preterm Birth, 2018–2021 are listed at the end of the article.

women do not receive the basic recommended interventions and number of visits.[3] The *Lancet Global Health* commission on 'High-Quality Health Systems in the Sustainable Development Goals Era' asserted that "Providing health services without guaranteeing a minimum level of quality is ineffective, wasteful, and unethical".[4]

Timing of birth is paramount, as the risk of neonatal death, severe morbidity, prolonged hospital admissions, and long-term sequelae increase the lower the gestational duration at preterm birth. Thus, up-to-date data of the local and global burden of preterm birth are critical for improving understanding about its epidemiology in order to support and target programs for reducing preterm birth rates over time and inform policies and resource allocation within health systems.

Evidence-based and data-driven improvements depend on accessible, accurate, and timely data actionable for pertinent stakeholders—from the local clinic to the global level, from local quality improvement to international science efforts. Health services data are often limited and outdated, and even the most basic data, such as preterm birth rates and mortality rates, are often based on estimations for global reporting purposes due to scarcity of country-level data. To better understand, prevent, and manage the excessive burden of preterm birth, there is a critical need for more timely data collection and use of health services data as actions should be based on evidence.

Recommendation: *FIGO calls for strengthening of health information systems for reproductive, maternal, newborn, and child health services, co-designed with users, to ensure the timely accessibility of actionable high-quality data for all stakeholders engaged in the prevention and management of preterm birth and its consequences.*

2 | DIGITAL REGISTRIES ALONG WITH CONTINUITY OF CARE

Every individual counts and should be counted individually. Opportunities and challenges for preventing and managing preterm birth exist along with the complete continuity of public health services and care for the mother–baby dyad—from pre-pregnancy care to pediatrics and onwards in life. These include preventive programs, such as well-woman health care, different models for antenatal care, and therapeutic care models, critical to preventing and managing preterm birth and its health outcomes. Along with this continuity, individual-level longitudinal data emerge and are needed to appropriately observe the quality and continuity of care provision, the prognosis of cohorts, and the denominators of outcome measures. Critically, such real-life registry data are needed for health technology assessments and post-implementation evaluations of predictive tests, therapeutic interventions, and preventive care models that may have efficacy in trial settings but uncertain effectiveness when implemented in new contexts at scale.

The 'WHO Guideline: Recommendations on Digital Interventions for Health System Strengthening' has summarized current state-of-the-art and recommended established digital health interventions to support adequate reproductive, maternal, newborn, and child health services in LMICs.[5] Among the digital health interventions recommended by the WHO Guideline Development Group is the digital tracking of clients' health status and services. Such digital health records that create a database of prospective, longitudinally collected data along with the continuity of care are recommended by the WHO with or without integrated digital health interventions for clinical decision support or targeted client communications (e.g. SMS messaging for reminders of care, test results, individualized health information). The leap from appropriate paper records to advanced health information systems has been seen as an impossible task for many LMICs—and the WHO recommendation comes with numerous contextual implementation considerations. Yet there is a certainty that paper is not the future of the information age. When digital tools are co-designed appropriately with end-users, they can limit the burden of data collection and maximize use of the data.[6] There is a rapidly increasing number of successful implementation experiences of maternal and child health and immunization registries across Latin America, sub-Saharan Africa, the Middle East, and South-East Asia. To facilitate implementation, the WHO has published complete suites of ready-made registry solutions in the reproductive, maternal, newborn, and child health area in the free, open-source system OpenSRP,[7] as has the worldwide community of practice of DHIS2, which is used as the health information system in over 70 LMICs.[8]

Recommendation: *FIGO calls for strengthening of investments and capacity for implementation of digital registries along with the continuity of reproductive, maternal, newborn, and child health services in line with WHO recommendations, and strengthening of the science of implementation and use of registries—from local quality improvement to big data exploration.*

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors and the members of the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. FF wrote

the first version of the manuscript. AB, ABM, and BJ revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version.

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SPECIAL ARTICLE

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FIGO good practice recommendations on modifiable causes of iatrogenic preterm birth

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Abstract

Iatrogenic preterm birth is a planned delivery that occurs before 37 weeks of gestation due to maternal and/or fetal causes. However, in some cases, such deliveries also occur with no apparent medical indication. The increasing numbers of iatrogenic preterm deliveries worldwide have led researchers to identify modifiable causes that allow the formulation of preventive strategies that could impact the overall preterm birth rate. The present document contains the FIGO (International Federation of Gynecology and Obstetrics) Working Group for Preterm Birth recommendations, aiming to reduce the rates of iatrogenic preterm birth based on four of the most common clinical scenarios and issues related to iatrogenic preterm delivery. The working group supports efforts to identify the contribution of iatrogenic preterm delivery to the overall preterm birth rate and encourages health authorities to establish preventive measures accordingly. We encourage care providers to maintain single embryo transfer policies to prevent multiple pregnancies as a substantial contributor of iatrogenic preterm birth. The working group also recommends that efforts to reduce unnecessary cesarean sections must be warranted, and mechanisms to ensure the appropriate time of delivery and strengthening of education and communication processes must be pursued.

KEYWORDS
elective delivery, iatrogenic preterm birth, modifiable causes

1 | INTRODUCTION

Iatrogenic preterm delivery, also called provider-initiated preterm birth, is defined as a birth that occurs before 37 weeks of gestation due to a planned delivery (induction of labor or cesarean section in the absence of spontaneous labor or rupture of membranes). According to reports, iatrogenic preterm delivery constitutes approximately 30%–35% of all preterm deliveries and may vary according to the region.[1-4] In the past decades, the rates of iatrogenic preterm deliveries have been increasing. As a result, it has become

* The Members of the FIGO Working Group for Preterm Birth, 2018–2021 are listed at the end of the article.

the leading cause of preterm delivery in some countries, reaching almost 50% of all preterm births.[2-5]

The causes of iatrogenic delivery vary according to the region of the world, but in general they can be divided into four main groups:

- obstetric complications (e.g. hypertensive disorders of pregnancy, placental conditions, antepartum hemorrhage)
- fetal causes (e.g. fetal distress, fetal growth restriction, structural malformations)
- maternal medical conditions (e.g. heart disease, nephropathy, cancer, sepsis)
- non-medically indicated iatrogenic preterm delivery.[2,5]

The incidence of iatrogenic preterm delivery is increasing worldwide. Some of the factors that may influence this phenomenon include the increase in maternal age, which is associated with more significant comorbidities and obstetric complications; the increase in the prevalence of obesity; the use of assisted reproductive techniques with the consequent rise in multiple pregnancies, which also carries an increased risk of obstetric complications in singleton pregnancies, including an increased rate of cesarean delivery—a risk factor for subsequent complications such as placenta previa and placenta accreta.[2,6] In addition, doctors' behavior also plays a role, as some obstetricians underestimate the risks of preterm delivery.

In some countries and regions, the main contributors of iatrogenic delivery have been identified and reported. For example, in China, causes such as hypertensive disorders of pregnancy, placenta previa, and multiple pregnancy are the most frequent, whereas in Brazil, hypertensive disorders of pregnancy, placental abruption, and diabetes play a significant role in the number of iatrogenic preterm births.[7,8] Based on these data, strategies have been proposed to address potentially modifiable risk factors for iatrogenic preterm delivery in order to reduce iatrogenic preterm delivery.[8,9]

2 | CLINICAL SCENARIOS AND ISSUES

2.1 | Iatrogenic preterm delivery for maternal, medical, and obstetric complications

Some pre-existing maternal conditions and obstetric complications may require delivery before 37 weeks of gestation to ensure the safety of the mother and/or the baby. However, the evidence supporting recommendations for the timing of delivery for most of these conditions is limited and primarily based on expert consensus. Therefore, this decision-making process often requires individualization. The prevalence of the different causes of iatrogenic preterm delivery varies depending on world region.[1,4] However, some of the most common maternal medical conditions and obstetric complications that may require indicated preterm birth are:

- hypertensive disorders of pregnancy
- placental and umbilical cord anomalies.

Preventing the conditions mentioned above is an ongoing challenge. Strategies such as reducing cesarean delivery rates would probably have an impact on the incidence of placenta previa or accreta; policies to reduce obesity in women would decrease the rates of gestational diabetes; and appropriate screening and use of low-dose aspirin in selected populations has been proven to reduce the prevalence of pre-eclampsia.[10] However, there are reasons to believe that doctors' attitudes and clinical behavior are the most critical factors.

Recommendation: Efforts should be directed to identifying the contribution of iatrogenic preterm delivery to the overall rate of preterm delivery and its causes in each country. We encourage health authorities to establish action plans, screening programs, evidence-based preventive measures, and health policies to target modifiable risk factors to prevent iatrogenic preterm delivery.

2.2 | Iatrogenic preterm delivery for fetal causes

Fetal development is a complex process that involves the interaction of genetic and environmental factors. Alterations at any step along the way can lead to fetal complications that may require early delivery to improve the chances of a healthy child. Fetal conditions such as fetal distress and fetal growth restriction secondary to impaired placental function and monochorionic multiple pregnancies are among the most common fetal causes of iatrogenic preterm delivery.

Preventing fetal causes of preterm delivery requires further research. However, assisted reproductive technologies have led to an increase in multiple pregnancies and, therefore, a related increase in preterm birth rates. Singleton pregnancies conceived using assisted reproductive technologies are also at increased risk of pregnancy complications. According to the Human Multiple Births Database, the global twin rate increased by a third (9.1 to 12.0/1000 deliveries) between 1980–1985 and 2010–2015.[11] The clinical impact of the increase of multiple pregnancies in terms of preterm birth, as reported by the Centers for Disease Control and Prevention (CDC), is that three of every five twin babies are born preterm (six times the rate for singletons) and one of every four preterm twins is admitted to the neonatal intensive care unit (five times the rate for singletons). Therefore, optimizing assisted reproductive technologies is a mandatory step toward reducing iatrogenic prematurity, particularly the adoption of single embryo transfer.

Recommendation: Continue and strengthen policies such as single embryo transfer to regulate assisted reproductive technologies worldwide, and promote and support research to understand and prevent fetal causes of preterm birth.

2.3 | Recommendation for the timing of iatrogenic delivery for common pregnancy conditions

While in each pregnancy the mother and fetus require individualized care, a general rule can be defined for common pregnancy

conditions. These rules are based on large randomized clinical trials conducted in recent years comparing induction of labor and expectant management. As is apparent from Table 1, iatrogenic delivery is not required for any of the common pregnancy conditions and appropriate monitoring is advised instead, perhaps with the exception of pre-eclampsia, in which delivery between 34 and 37 weeks can be considered,[12,13] while for women with chronic hypertension the recommendation based on non-randomized data is 38 weeks.[14] In pregnancies complicated by growth restriction at term, the DIGITAT study showed that the optimal timing of induction is around 38 weeks,[15] while in pregnancies with early-onset growth restriction without fetal distress, earlier induction does not improve outcomes.[16] Similarly, for pregnancies complicated by macrosomia, induction of labor at 38 weeks improved outcomes compared to expectant management.[17] While RCTs are lacking for studies complicated by diabetes, it can be assumed that in the presence of macrosomia, induction of labor at 38 weeks improves outcomes.

For pregnancies complicated by preterm prelabour rupture of membranes (PPROM) without GBS or other signs of infection, expectant management until 37 weeks improves neonatal respiratory outcomes.[18] Careful monitoring for signs of infection is warranted as women with PPROM between 34 + 0/7 and 36 + 6/7 weeks who undergo expectant management are more likely to have an antepartum hemorrhage or chorioamnionitis.[18] For women with uncomplicated twin pregnancies, individual participant data meta-analysis of cohort studies shows the optimal timing of delivery to be 37 weeks for dichorionic pregnancy and 37 weeks + 0 days for monochorionic pregnancy.[19] Finally, in women with uncomplicated singleton pregnancies, two large RCTs definitively showed that induction of labor should be offered at 41 weeks,[20] whereas the ARRIVE study suggests that induction of labor at 39 weeks improves outcomes.[21]

Three things should be stressed. First, and most important, these are general rules of thumb for pregnancies complicated by a condition but with otherwise non-compromised mother and fetuses. Of course, individual findings regarding the condition of the mother or fetus justify earlier delivery. Second, apart from pre-eclampsia, all recommended gestational ages are at or beyond 37 weeks, which should stimulate careful consideration around scheduling women for iatrogenic preterm delivery. Third, it should be considered that progression of pregnancy, in general, improves cognitive performance of the offspring.[22]

2.4 | Previous cesarean delivery and preterm delivery

Cesarean delivery (CD) rates have increased worldwide over the past decades, particularly in middle- and high-income countries. It has been reported that between 1990 and 2014 the global average CD rate increased 12.4% (from 6.7% to 19.1%), with an average annual increase of 4.4%.[23] In the secondary analysis of the Multicountry Survey on Maternal and Newborn Health (WHOMCS), the WHO has demonstrated that previous cesarean deliveries are associated with increased risk of preterm birth and complications that lead to preterm delivery, such as uterine rupture (aOR 7.7; 95% CI 5.5–10.9), morbidly adherent placenta (aOR 2.6; 95% CI 2.0–3.4), and placenta previa (aOR 1.8; 95% CI 1.5–2.1).[23,24]

The reasons for the increase in cesarean rates are multifactorial and poorly understood. However, factors that may play an essential role for some countries are health systems dynamics and limited resources, making caesarean delivery a more convenient mode of delivery, sociocultural issues like women's fear of pain or pelvic relaxation after vaginal delivery, and maternal and clinician preferences.

Recommendation: To reduce preterm delivery related to previous cesarean complications, efforts should be made on a multilevel basis to avoid unnecessary cesarean sections.

3 | NONMEDICALLY-INDICATED PRETERM DELIVERY

In some studies, and particularly in low- and middle-income countries, there is a significant percentage of iatrogenic deliveries between 34 and 36 weeks.[4,5] However, a clear indication is not always recorded. This happens due to the absence of, or lack of adherence

TABLE 1 Indicative gestational age of delivery for different pregnancy complications

Condition	Gestational age recommended for planned delivery	Evidence from literature
Pregnancy-induced hypertension	39 weeks	HYPITAT I and II[12]
Pre-eclampsia	34–37 weeks	HYPITAT I and II[12] Phoenix[13]
Chronic hypertension	38 weeks	Population-based study[14]
Fetal growth restriction without fetal distress	38 weeks	DIGITAT,[15] GRIT[16]
Large baby (including diabetes)	38 weeks	DAME[17]
Preterm Prelabour Rupture of Membranes (PPROM) (without GBS)	37 weeks	PROMPT, PROMEXIL I & II[18]
Uncomplicated dichorionic twin pregnancy	37 weeks	Individual participant data meta-analysis[19]
Uncomplicated monochorionic twin pregnancy	37 weeks and 0 days	Individual participant data meta-analysis[19]
Uncomplicated singleton pregnancy	41 weeks	Index and Swepis,[20] ARRIVE[21]

to, clinical practice guidelines, or practice based on personal experience rather than evidence-based for the treatment of medical complications. It is well known that the morbidity of a late preterm infant born between 34 and 36 weeks of gestation is seven times greater than a full-term infant.[1,2] Therefore, the decision to deliver a preterm infant should balance the risks of morbidity and perinatal mortality of prematurity against the possible maternal and fetal consequences of continuing a pregnancy. One of the strategies aiming to reduce the number of late iatrogenic preterm and early-term births is elective induction of labor and elective cesarean section after 39 weeks of gestation.[25] This policy has been adopted and proven successful in countries like the United States.[26]

Another cause of iatrogenic preterm delivery could be the lack of appropriate dating of pregnancy. It is well known that the first trimester ultrasound, when performed by properly trained personnel, constitutes the most accurate method to estimate gestational age. However, in the absence of a proper ultrasound examination before 22 + 0 weeks of gestation, the pregnancy is considered as suboptimally dated and therefore at greater risk for iatrogenic preterm birth.[27]

Recommendation: Mechanisms for implementing and ensuring a first trimester ultrasound for appropriate dating of pregnancy as well as adherence to clinical practice guidelines for appropriate delivery timing in different medical, fetal, and obstetrical conditions should be considered. Strengthening the patient education and communication processes to achieve good decision-making processes must be pursued.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. CM wrote the first version of the manuscript. BWM and BJ revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version of the manuscript.

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SPECIAL ARTICLE

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FIGO good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minimize harm in babies born preterm

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Abstract

For women with a singleton or a multiple pregnancy in situations where active neonatal care is appropriate, and for whom preterm birth is anticipated between 24 and 34 weeks of gestation, one course of prenatal corticosteroids should ideally be offered 18 to 72 h before preterm birth is expected to improve outcomes for the baby. However, if preterm birth is expected within 18 h, prenatal corticosteroids should still be administered. One course of corticosteroids includes two doses of betamethasone acetate/phosphate 12 mg IM 24 h apart, or two doses of dexamethasone phosphate 12 mg IM 24 h apart. In women in whom preterm birth is expected within 72 h and who have had one course of corticosteroids more than a week previously, one single additional course of prenatal corticosteroids could be given at risk of imminent delivery. Prenatal corticosteroids should not be offered routinely to women in whom late preterm birth between 34 and 36 weeks is anticipated. In addition, prenatal corticosteroids should not be given routinely before cesarean delivery at term. Neither should prenatal corticosteroids be given "just in case". Instead, prenatal steroid administration should be reserved for women for whom preterm birth is expected within no more than 7 days, based on the woman's symptoms or an accurate predictive test.

KEYWORDS
"just in case treatment", antenatal, betamethasone, child outcome, corticosteroids, dexamethasone

1 | INTRODUCTION

The first randomized trial of prenatal corticosteroids to reduce respiratory distress syndrome in babies subsequently born preterm was published in 1972.[1] Evidence of their efficacy has been accumulating since then, and since the mid-1980s prenatal corticosteroids have been increasingly used for this indication. The robust evidence for their effectiveness in this regard has led many authorities worldwide to endorse their use to improve outcomes for the baby.[2]

While the lung maturational effects of a single course of corticosteroids are apparent, there are emerging concerns of potential harm; for example, when multiple courses are applied, when women given prenatal corticosteroids deliver at term rather than preterm, or

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when corticosteroids are given in unproven scenarios such as elective cesarean section at term.

The purpose of this document is to review the evidence and provide good practice recommendations for the use of prenatal corticosteroids to improve outcomes in babies likely to be born preterm.

2 | CLINICAL SCENARIOS AND DRUG ADMINISTRATION

2.1 | *Singleton pregnancy where preterm birth is anticipated before 34+0 weeks of gestation*

Meta-analysis of 27 trials evaluating one or more courses of prenatal corticosteroids (betamethasone, dexamethasone, or hydrocortisone) in comparison with placebo or no treatment in babies anticipated to be born preterm has shown clear benefits for the baby, with a reduction in perinatal death (RR 0.85; 95% CI 0.77–0.93), respiratory distress syndrome (RR 0.71; 95% CI 0.65–0.78), intraventricular hemorrhage (RR 0.58; 95% CI 0.45–0.75), necrotizing enterocolitis (RR 0.50; 95% CI 0.32–0.78), and developmental delay in childhood (RR 0.51; 95% CI 0.27–0.97), but not cerebral palsy.[3] Potential harms included evidence of reduced glucose tolerance but not diagnoses of diabetes in offspring exposed to prenatal corticosteroids in utero.

For trials in this meta-analysis, the steroid most commonly used was a betamethasone acetate/phosphate mix, in a dose of 24 mg divided across 24 h. The majority of studies used a single course of steroids. The majority of trials included women with ruptured membranes. There was no evidence that ruptured membrane status led to any differences in fetal outcomes or rates of chorioamnionitis or endometritis. There is some evidence that different types of corticosteroid have different effects on chorioamnionitis, but no evidence of difference in outcome for the baby.[3]

Betamethasone, but probably not dexamethasone, appears to reduce chorioamnionitis (RR 0.69; 95% CI 0.51–0.93). However, the Cochrane review suggests fewer benefits of corticosteroids when administered at or after 35+0 weeks.[3] Additionally, the National Institute for Health and Care Excellence (NICE) in the UK notes that the evidence for benefit over harms of prenatal steroid use is strongest for babies born between 24+0 and 34+0 weeks of gestation.[4] Therefore, the lower limit for offering prenatal corticosteroids should be adjusted to the time when active care is appropriate in each specific location.

Recommendation: *For women with singleton pregnancies where active neonatal care is appropriate, for whom preterm birth is anticipated between 24+0 and 34+0 weeks of gestation, prenatal corticosteroids should be offered to improve outcomes for the baby.*

2.2 | *Multiple pregnancy where preterm birth is anticipated before 34+0 weeks of gestation*

There is much less evidence on the impact of prenatal corticosteroids in multiple pregnancies: the number of babies evaluated in trials restricted to multiple pregnancies is fewer than 250 for the outcomes of fetal, perinatal, or neonatal death, and 320 for the outcome of respiratory distress syndrome.[3,5] However, the effect size is similar for all mother and baby outcomes, regardless of whether the study recruited women with singleton, multiple pregnancy, or a mixed population.

Recommendation: *For women with multiple pregnancy where active neonatal care is appropriate, for whom preterm birth is anticipated between 24+0 and 34+0 weeks of gestation, prenatal corticosteroids should be offered to improve outcomes for the baby.*

2.3 | *Pregnancies where late preterm birth between 34+0 and 36+6 weeks of gestation is anticipated*

A high-quality US study assessed the effects of corticosteroids in 2831 women at risk of late preterm birth (34+0 until 36+5 weeks of gestation).[6] The administration of corticosteroids statistically significantly reduced the requirement for respiratory support in the first 72 h of life (11.6% vs 14.4%; RR 0.80; 95% CI 0.66–0.97; number needed to treat = 36). However, neonatal hypoglycemia was more common in the betamethasone group than in the placebo group (24.0% vs 15.0%; RR 1.6; 95% CI 1.37–1.87; number needed to harm = 11). While no long-term harms have been proven following corticosteroids at late preterm gestations, there has been no significant follow-up of trials. Observational studies using population data have shown prenatal corticosteroid exposure is associated with increased behavioral and psychiatric diagnoses in children.[7]

Recommendation: *Prenatal corticosteroids should not be offered routinely to women in whom late preterm birth is anticipated. Instead, the use of prenatal corticosteroids should be considered in light of the balance of risks and benefits for individual women.*

3 | TYPE AND DOSE OF PRENATAL CORTICOSTEROIDS

Most studies have used betamethasone acetate/phosphate or dexamethasone phosphate as the prenatal steroid.[3] Typical treatment regimens (one course) are two doses of betamethasone acetate/phosphate 12 mg intramuscularly 24 h apart, or four doses of 6 mg dexamethasone phosphate intramuscularly 6 h apart. However, other treatment regimens have been used. It is vital to use an effective steroid formulation and the correct dose regimen for the type of steroid used to ensure sustained fetal exposure to the agent.[8] Assuming this is achieved, there is no evidence that either is better for reducing fetal or neonatal adverse outcomes. The Asteroid study randomized 1356 women to two intramuscular injections of either 12 mg dexamethasone (dexamethasone sodium phosphate) or 11.4 mg betamethasone (Celestone Chronodose) 24 h apart, and found no differences in two-year outcomes between the two groups.[9] As mentioned above, the relative risk of maternal chorioamnionitis appears lower with betamethasone acetate/phosphate.[3]

Recommendation: *Where prenatal corticosteroids are given to improve fetal outcomes, appropriate regimens include two doses of betamethasone acetate/phosphate 12 mg (=one course) IM 24 h apart, or*

two doses of dexamethasone phosphate 12mg (=one course) IM 24 h apart.

4 | TIMING OF ADMINISTRATION

No large randomized trials compare different planned time intervals between prenatal corticosteroid administration and preterm birth. Retrospective studies have suggested that composite mortality and morbidity are lowest where the birth occurs 18–36 h after prenatal steroid administration, although some benefit was observable within 3 h.[10] Reduction in severe brain injury was most significant where the birth occurred 48–72 h after steroid administration. Almost all benefits of prenatal steroid administration had disappeared if the birth occurred 1 week or later after steroid administration.

Recommendations: *Prenatal corticosteroids should ideally be given 18–72 h—and certainly no more than 1 week—before preterm birth is anticipated. However, if preterm birth is expected within 18 h, prenatal corticosteroids should still be administered*.

5 | SINGLE OR MULTIPLE COURSES OF CORTICOSTEROIDS

Animal studies demonstrate the adverse effect of multiple courses of prenatal corticosteroids on the birthweight of the baby and subsequent hypothalamic-pituitary-adrenal axis function and neuronal myelination.

Ten trials have compared a repeat course of corticosteroids with no treatment in women who remain at risk of preterm birth 7 or more days after an initial course.[11] A repeat course of corticosteroids reduced the risk of respiratory distress syndrome (RR 0.83; 95% CI 0.75–0.91) and severe infant outcome (RR 0.84; 95% CI 0.75–0.94). There was a reduction in birthweight (mean difference of −75.79 g; 95% CI −117.63 to −33.96 g) but no difference in birthweight outcomes adjusted for gestational age. The follow-up to early childhood (18–24 months) showed no impact, including no effect on outcomes of total deaths, disability-free survival, serious outcome, or growth. No significant positive or negative effects were apparent for the mother. An individual patient data meta-analysis showed broadly similar results, with corticosteroids associated with a substantial reduction in birthweight z scores.[12]

Recommendations: *In women in whom preterm birth is expected within 72 h and who have had one course of corticosteroids more than a week ago, one additional course of prenatal corticosteroids could be given to improve outcomes for the baby*.

6 | USE OF PRENATAL CORTICOSTEROIDS IN LOW-RESOURCE SETTINGS

The initial randomized trials evaluating the benefits of prenatal corticosteroids have been conducted in high-income settings. It had been assumed that the results of these studies were generalizable to all settings. However, the ACT cluster-randomized trial conducted in Argentina, Guatemala, India, Kenya, Pakistan, and Zambia demonstrated that prenatal corticosteroids did not reduce the primary outcome of neonatal mortality in babies below the 5th centile for birthweight (RR 0.96; 95% CI 0.87–1.06).[13] Suspected maternal infection was increased in the intervention group (OR 1.67; 95% CI 1.33–2.09) and neonatal mortality across the entire intervention group (a secondary outcome) was increased (RR 1.12; 1.02–1.22). Reassuringly, a subsequent trial "ACTION", conducted in 29 hospitals across Bangladesh, India, Kenya, Nigeria, and Pakistan, has unequivocally shown that prenatal dexamethasone given from 24–34 weeks of gestation does improve outcome, reducing stillbirth and neonatal death (RR 0.88; 95% CI 0.78–0.99) without increasing maternal infection.[14] Rates of preterm birth were higher in ACTION than in ACT, and women were only included if gestational age had been confirmed by ultrasound. Data from ACTION are included in the latest Cochrane meta-analysis, which ensures the benefit of prenatal corticosteroids in low-resource settings.[3] The lower limit for offering prenatal corticosteroids should be adjusted to the time at which active care is appropriate at the specific location.

Recommendation: *In low-resource settings, prenatal steroids should be given to women with a singleton pregnancy where active neonatal care is appropriate and preterm birth is anticipated from 24–34 weeks of gestation, when ideally the following conditions are met: gestational age assessment can be accurately undertaken, preterm birth is considered imminent, there is no clinical evidence of maternal infection, adequate childbirth care is available (including the capacity to recognize and safely manage preterm labor and birth), the preterm newborn can receive adequate care if needed (including resuscitation, thermal care, feeding support, infection treatment, and safe oxygen use)*.

7 | BABIES BORN BY CESAREAN SECTION AT TERM

Three studies (1196 participants) have examined the impact of corticosteroids before cesarean section at term (≥39 weeks of gestation; data taken from a wider meta-analysis of corticosteroids prior to elective cesarean section).[15] There was no statistically significant effect on respiratory distress syndrome (RR 0.45; 95% CI 0.07–3.07), although only four of the 1196 babies had respiratory distress syndrome, nor were there any effects on transient tachypnoea of the newborn or other respiratory events. In addition, all three included studies had inadequate blinding of participants and/or personnel, leading to concern about potential bias. [Correction added on 14-February 2022 after first online and print publication: The preceding sentence has been amended in this version.]

Recommendation: *Prenatal corticosteroids should not be given routinely before cesarean section at term*.

8 | PRENATAL CORTICOSTEROIDS AS A "JUST IN CASE" THERAPY

Given the undoubted short-term benefits of corticosteroids for babies delivering preterm ≤34+0 weeks of gestation within 7 days

(ideally 48 h) of steroid administration, clinicians may be tempted to give them "just in case" to women at high risk. However, there is no evidence that such a strategy is beneficial for babies in the short term. This lack of benefit has to be balanced against the evidence that corticosteroids can cause long-term harm to babies, particularly to those babies who are subsequently born at term. For example, a population cohort from Finland of over 4000 pairs of term-born siblings discordant for steroid exposure demonstrated a hazard ratio of 1.33 (95% CI 1.26–1.41) for mental and behavioral disorders.[7]

Recommendation: Prenatal corticosteroids should not be given "just in case." Prenatal steroid administration should be reserved for women for whom preterm birth is expected within no more than 7 days, based on the woman's symptoms (including contractions or preterm prelabor membrane rupture) or an accurate predictive test.

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AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. SJS and JN wrote the first version of the manuscript. AS and BJ revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version.

MEMBERS OF THE FIGO WORKING GROUP FOR PRETERM BIRTH, 2018–2021

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SPECIAL ARTICLE

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FIGO good practice recommendations on cervical cerclage for prevention of preterm birth

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Abstract

Cervical cerclage is an intervention which when given to the right women can prevent preterm birth and second-trimester fetal losses. A history-indicated cerclage should be offered to women who have had three or more preterm deliveries and/or mid-trimester losses. An ultrasound-indicated cerclage should be offered to women with a cervical length <25 mm if they have had one or more spontaneous preterm birth and/or mid-trimester loss. In high-risk women who have not had a previous mid-trimester loss or preterm birth, an ultrasound-indicated cerclage does not have a clear benefit in women with a short cervix. However, for twins, the advantage seems more likely at shorter cervical lengths (<15 mm). In women who present with exposed membranes prolapsing through the cervical os, a rescue cerclage can be considered on an individual case basis, taking into account the high risk of infective morbidity to mother and baby. An abdominal cerclage can be offered in women who have had a failed cerclage (delivery before 28 weeks after a history or ultrasound-indicated [but not rescue] cerclage). If preterm birth has not occurred, removal is considered at 36–37 weeks in women anticipating a vaginal delivery.

KEYWORDS
cerclage, intra-abdominal cerclage, preterm birth, prevention

1 | INTRODUCTION

Cervical cerclage is a commonly performed intervention in the care of women at risk of preterm birth and second-trimester fetal loss. A suture is placed in the cervix to prevent preterm dilatation. There remains uncertainty surrounding the population of women who are most likely to benefit and the optimal surgical techniques to be used. Several randomized controlled trials (RCTs) and meta-analyses have been undertaken to help provide an evidence-based approach to management.

1.1 | Type of cerclage

Cerclages can be categorized by the indication for insertion:

1. History-indicated, performed in asymptomatic women with risk factors in the obstetric or gynecologic history that increase the risk of preterm birth.
2. Ultrasound-indicated, performed on asymptomatic women with cervical shortening.
3. Rescue cerclage, where the cervix is already open and the fetal membranes exposed.

* The Members of the FIGO Working Group for Preterm Birth, 2018–2021 are listed at the end of the article.

Vaginal cerclage insertion, either ultrasound- or history-indicated, is not associated with an increased risk of preterm prelabor rupture of membranes, chorioamnionitis, or cesarean section.[1-3]

2 | ASYMPTOMATIC WOMEN WITH A PREVIOUS HISTORY OF PRETERM BIRTH

History-indicated cerclages have been shown to be beneficial in specific populations. A pre-specified subgroup analysis of an international multicenter trial encompassing 1292 women indicated benefit from a cerclage, inserted prophylactically during the first trimester, in women who had undergone three or more previous preterm births and/or second-trimester losses. The preterm birth rate before 33 weeks of gestation was halved in women who had undergone cerclage (15% vs 32%). This effect was not observed in women with two or fewer previous preterm deliveries. Where women had had one previous preterm birth, the rate of preterm birth before 33 weeks was 14% versus 17% in the expectant group. Where women had undergone two previous preterm deliveries, the rate of preterm birth was 12% in the cerclage group versus 14% in the expectant group.[1]

Recommendation: *A history-indicated cerclage should be offered in women who have had three or more preterm deliveries and/or mid-trimester losses*.

3 | ASYMPTOMATIC WOMEN WITH A SHORT CERVIX

Where high-risk women undergo ultrasound surveillance of cervical length and cervical shortening <25 mm is identified, a cerclage has been found to be beneficial when inserted at gestations less than 24 weeks. A meta-analysis including data from four RCTs indicated that an ultrasound-indicated cerclage for a cervical length <25 mm in women who had had one or more spontaneous mid-trimester losses or preterm births reduced the incidence of birth before 35 weeks (RR 0.57; 95% CI 0.33–0.99 in women who had a previous second-trimester loss, and RR 0.61; 95% CI 0.4–0.92 in women with a previous preterm birth before 36 weeks of gestation).[2]

Recommendation: *An ultrasound-indicated cerclage should be offered to women with a cervical length <25 mm if they have had one or more spontaneous preterm birth and/or mid-trimester loss*.

4 | ASYMPTOMATIC WOMEN WITH OTHER RISK FACTORS OR MÜLLERIAN ABNORMALITIES

The role of history- or ultrasound-indicated cerclage is less evident in other high-risk groups such as women with Müllerian abnormalities or cervical surgery, as there have been only preliminary studies to inform practice.[4] A meta-analysis of 27 retrospective cohort studies showed an increased risk of preterm birth <37 weeks of gestation when cold knife conization was compared with no treatment (14% vs 5%; RR 2.59; 95% CI 1.8–3.72) and LLETZ versus no treatment (11% vs 7%; RR 1.24; 95% CI 1.14–1.35.[5] In women with a short cervix and history of cervical surgery, management should be individualized, but some clinicians consider cerclage with a cervical length <25 mm. There is a lack of randomized controlled trials to support the use of either ultrasound- or history-indicated cerclage in women with multiple pregnancies[6] without additional risk factors. If cerclage is considered in a twin pregnancy, observational evidence suggests that benefit is more likely with a shorter cervix (<15 mm).[7] If a cervix is incidentally noted as short in a low-risk population, no benefit appears to be conferred from an ultrasound-indicated cerclage.[4-8]

Recommendation: *In high-risk women who have not had a previous mid-trimester loss or preterm birth, an ultrasound-indicated cerclage does not have a clear benefit in women with a short cervix but can be considered on an individual case basis. For twins, the advantage seems more likely at shorter cervical lengths (<15 mm).*

5 | WOMEN WITH CERVICAL SHORTENING AND DILATATION THAT HAVE ALREADY RESULTED IN FETAL MEMBRANE EXPOSURE

Where cervical shortening and dilatation have already resulted in fetal membrane exposure, the insertion of a rescue cerclage can be considered before 24 weeks of gestation, where it may delay birth compared with expectant management/bed rest alone. Overt infection (intra-amniotic infection and/or inflammation) or active labor are contraindications to insertion. Infection and inflammation can first be explored under particular circumstances with amniocentesis, but a non-invasive test is warranted and needs to be developed.[9-11] A systematic review, including one RCT and prospective and retrospective cohort studies, has indicated insertion of a rescue cerclage is associated with increased neonatal survival and prolongation of pregnancy. Birth at all gestations after 24 weeks was reduced.[12] Further prospective RCTs are required to evaluate the risks and benefits of rescue cerclage.

Recommendation: *In women who present with exposed membranes prolapsing through the cervical os, a rescue cerclage can be considered on an individual case basis, taking into account the high risk of infective morbidity to mother and baby.*

6 | ASYMPTOMATIC WOMEN WITH PREVIOUS UNSUCCESSFUL CERCLAGE

In high-risk women who have previously undergone an unsuccessful cerclage, a transabdominal cerclage can be inserted in situations with adequate operative resources. The suture is inserted via the abdomen, more proximally. Its use is supported by evidence from a multicenter RCT of transabdominal cerclage versus a vaginally placed high or low cervical cerclage that rates of preterm birth <32 weeks of gestation and fetal losses were lower (8% vs 33%; RR 0.33; 95% CI 0.07–0.76)

in women who received transabdominal cerclage.[13] There were also fewer fetal losses (3% vs 21%; RR 0.12; 95% CI 0.016–0.93). In this trial preterm birth rates <32 weeks were similar in women receiving high or low vaginal cerclage (38% vs 33%). This can be placed either at laparotomy or laparoscopy.[14] Pre-conceptual insertion should be considered when possible due to reduced anesthetic risks and the technical advantages of operating on a non-pregnant uterus. There is no evidence that pre-conceptual placement has a detrimental effect on fertility or the management of early miscarriage. A link to a video of the procedure is given in Suff et al.[15]

Recommendation: *In women who have had a failed cerclage (delivery before 28 weeks after a history- or ultrasound-indicated [but not rescue] cerclage), an abdominal cerclage can be offered.*

7 | OTHER ISSUES REGARDING CERCLAGE

7.1 | Surgical technique

The choice of cerclage material and specific technique of insertion should be at the discretion of the surgeon. There is currently insufficient evidence to support any particular technique. However, randomized comparisons of vaginal cerclage (Shirodkar versus McDonald) have shown similar outcomes.[13,16] However, they should be placed as high as practically possible.[17] Abdominal cerclage can be performed preconceptually or laparoscopically, although there is no evidence to support a specific technique or timing. Infertility is not affected by abdominal cerclage.

7.2 | Perioperative considerations

Regional or general anesthesia is required for cerclage insertion (including abdominal cerclage). There is no evidence that a specific anesthetic has any advantage. Routine catheterization is not required and depends on the anesthetic and surgeons' discretion. Vaginal cerclage can usually be removed without additional anesthesia unless buried or high. Vaginal cerclage can be performed as a day case, but inpatient management may be required if sepsis is suspected following rescue cerclage. A retrospective survey of 226 women compared inpatient vs. outpatient management; there was no benefit in inpatient procedures with 48 h of admission.[18]

7.3 | Cerclage removal

If preterm birth has not occurred, removal is considered at 36–37 weeks in women anticipating a vaginal delivery. With preterm rupture of membranes, there is no evidence that the suture will improve outcomes, so removal is at the discretion of the clinician and patient taking into account the potential balance of prolonging the gestation with the potential risk of chorioamnionitis.

7.4 | Adjuvant/alternative therapy

Several different therapies have been advocated before or at the time of cerclage. These include tocolysis (usually indomethacin), antibiotics, and amnioreduction. All these interventions lack high-quality prospective evidence of benefit and can be considered on an individual case basis. Multiple studies have compared different agents (progesterone, pessaries, and cerclage) to prevent preterm birth. Several randomized controlled trials are in progress comparing the three treatments.[19,20] There is also currently no evidence to support the use of these interventions simultaneously.[21]

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. Lisa Story reports receipt of equipment, materials, drugs, medical writing, gifts or other services from Clinical Innovations. Bo Jacobbson 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 expendidures reimbused 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 Jacobbson 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. William Grobman reports no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept of the paper. AS and LS wrote the first version of the manuscript. BJ and WAG revised various versions of the manuscript. All authors and Working Group members commented on the manuscript and approved the final version.

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SPECIAL ARTICLE

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FIGO good practice recommendations on magnesium sulfate administration for preterm fetal neuroprotection

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Abstract

In women at risk of early preterm imminent birth, from viability to 30 weeks of gestation, use of MgSO4 for neuroprotection of the fetus is recommended. In pregnancies below 32–34 weeks of gestation, the use of MgSO4 for neuroprotection of the fetus should be considered. MgSO4 should be administered regardless of the cause for preterm birth and the number of babies in utero. MgSO4 should be administered when early preterm birth is planned or expected within 24 h. When birth is planned, MgSO4 should commence as close as possible to 4 h before birth. If delivery is planned or expected to occur sooner than 4 h, MgSO4 should be administered, as there is still likely to be an advantage from administration within this time. The optimal regimen of MgSO4 for fetal neuroprotection is an intravenous loading dose of 4 g (administered slowly over 20–30 min), followed by a 1 g per hour maintenance dose. This regimen should continue until birth but should be stopped after 24 h if undelivered. When MgSO4 is administered, women should be monitored for clinical signs of magnesium toxicity at least every 4 h by recording pulse, blood pressure, respiratory rate, and deep tendon (for example, patellar) reflexes.

KEYWORDS
antenatal, child outcome, magnesium sulfate, neuroprotection

1 | INTRODUCTION

The prevalence of cerebral palsy is increasing, related to an increase in early gestation survival.[1] Twenty-five percent of all cerebral palsy cases occur in babies born before 34 weeks of gestation.[2] Observational data from studies examining the use of magnesium sulfate (MgSO4) for tocolysis and for treating preeclampsia first indicated the potential neuroprotective effects for preterm infants.[3]

Subsequent randomized controlled trials to assess the role of MgSO4 in preterm fetal neuroprotection were analyzed in a Cochrane review in 2009. This meta-analysis concluded that antenatal MgSO4 therapy given to women at risk of early preterm birth (under 34 weeks) reduces the risk of cerebral palsy in their children (RR 0.68, 95% CI 0.54–0.87; five trials, 6145 infants).[4] In addition, in an individual participant data meta-analysis, antenatal MgSO4 reduced the combined risk of death or cerebral palsy (RR 0.86, 95% CI 0.75–0.99) with an NNT of 41 women (to reduce a combination of death and both moderate and severe types of cerebral palsy).[5] MgSO4 is an inexpensive drug; however, setting up and monitoring magnesium sulfate infusions incurs additional medical staff time. Nevertheless, training time should be minimal, as most units have experience with MgSO4 infusion for eclampsia prevention.

* The Members of the FIGO Working Group for Preterm Birth, 2018–2021 are listed at the end of the article.

2 | GESTATIONAL AGE AT WHICH MgSO4 IS GIVEN

All women in the 2009 Cochrane review were given MgSO4 at <34 weeks of gestation, with 68% of women <30 weeks of gestation.[4] Cerebral palsy is inversely related to gestational age; therefore, the absolute risk difference from treatment is likely to be larger at earlier gestations. Correspondingly, numbers needed to treat will be smaller earlier in pregnancies and higher at later gestational ages.

Recommendation: In women at risk of early preterm imminent birth, from viability to 30 weeks of gestation, use of MgSO4 for neuroprotection of the fetus is recommended. In women at risk of early preterm imminent birth, <32–34 weeks of gestation, the use of MgSO4 for neuroprotection of the fetus should be considered.

3 | OPTIMAL TIMING FOR MgSO4 ADMINISTRATION

In two of the four trials included in the Cochrane review, MgSO4 was given when birth was expected or planned within 24 h.[6,7] Subgroup analyses of these trials showed a RR of 0.81 (0.68–0.97) of death or cerebral palsy.[4] The median time from randomization to birth in the MgSO4 group of these two trials was between 1.6 and 3.7 h.

It has been previously shown that antenatal infusions enable the prompt transfer of MgSO4 to the mother (within 30 min) and that neonatal magnesium sulfate concentrations remained elevated up to 24 h. This indicates that MgSO4 crosses the placenta to the fetus promptly after commencing the infusion.

Recommendation: MgSO4 should be administered when early preterm birth is planned or expected within 24 h. When birth is planned, MgSO4 should commence as close as possible to 4 h before birth. If delivery is planned or expected to occur sooner than 4 h MgSO4 should be administered, as there is still likely to be an advantage from administration within this time.

4 | OPTIMAL REGIMEN FOR MgSO4 ADMINISTRATION

The dose of MgSO4 differed between studies, with loading doses varying between 4 g and 6 g, and inconsistency in whether a maintenance dose was administered. A meta-analysis concluded that although the beneficial effect of MgSO4 persisted in the studies using lower overall doses, there is currently insufficient evidence to define a minimum effective dose or optimal regimen for administration.[2] Magnesium toxicity is unlikely at the dose recommended below, and serum magnesium monitoring is not routinely recommended.

Recommendation: In women at risk of early preterm birth, use magnesium sulfate for neuroprotection of the fetus:

- *intravenously with a 4 g loading dose (administered slowly over 20–30 min)*
- *1 g per hour maintenance dose via the intravenous route*
- *continue regimen until birth, but stop after 24 h if undelivered.*

5 | MgSO4 ADVERSE EFFECTS

Magnesium sulfate produces flushing, sweating, and a sensation of warmth due to its peripheral vasodilator effects when infused intravenously. Other reported maternal side effects related to dosage and speed of infusion include nausea, vomiting, headache, palpitations and, rarely, pulmonary edema. Overdose can result in cardiac and neurological adverse events. There is no evidence of any unintended adverse outcomes in the neonate.[8] MgSO4 was initially considered as a tocolytic; however, there is no evidence that delivery is delayed when used.

Recommendation: Where MgSO4 is administered, monitor women for clinical signs of magnesium toxicity at least every 4 h by recording pulse, blood pressure, respiratory rate, and deep tendon (for example, patellar) reflexes.

6 | EFFICACY OF MgSO4 IN SUBGROUPS

MgSO4 is beneficial for fetal neuroprotection in spontaneous and iatrogenic preterm births, with no apparent differences in treatment effects among the subgroups (including pre-eclampsia, spontaneous PTB, PPROM, chorioamnionitis, and antepartum hemorrhage).[6] All trials in the Cochrane review included twins, with two of the four trials including high-order multiples, and showed evidence of benefit.[4]

Recommendation: In women at risk of imminent preterm birth, MgSO4 should be used for neuroprotection of the fetus, regardless of the cause for preterm birth and the number of babies in utero.

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. Natalie Suff reports no conflicts of interest. Bo Jacobbson 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 expendidures reimbused 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 Jacobbson 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.

AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. AS and NS wrote the first version of the manuscript. BJ and JN revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version.

MEMBERS OF THE FIGO WORKING GROUP FOR PRETERM BIRTH, 2018–2021

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SPECIAL ARTICLE

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FIGO good practice recommendations on the use of pessary for reducing the frequency and improving outcomes of preterm birth

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Abstract

A pessary is a device made of synthetic material that is placed in the vagina and has been used for prevention of preterm birth. It has been suggested that a potential mechanism of the pessary is alteration of the cervico-uterine angle to a more posterior position, which reduces cervical compression in women with a singleton pregnancy and a short cervical length. Pessaries should not be used in routine clinical care to reduce the frequency of preterm birth or to improve outcomes (e.g. neonatal outcomes) related to preterm birth. In women with a twin pregnancy—regardless of cervical length—pessaries should not be used in routine clinical care to reduce the frequency of preterm birth or to improve outcomes (e.g. neonatal outcomes) related to preterm birth. Presently there is no sufficient evidence suggesting that pessaries should be used as a standard treatment to prevent preterm birth; their use should be reserved for study populations.

KEYWORDS
antenatal, child outcome, pessary, singleton, twin

1 | INTRODUCTION

A pessary is a device made of synthetic material that is placed in the vagina. One potential application of the pessary has been preventing preterm birth in high-risk groups, such as women with a singleton pregnancy with a shortened cervix in the mid-gestation, or those with a twin gestation. One hypothesis is that the pessary alters the cervico-uterine angle to a more posterior position, which reduces cervical compression and other changes. Nevertheless, the exact physiologic mechanism by which a more posterior cervix would lead to a lower preterm birth rate has not been demonstrated.

There have been several randomized trials within the last decade (and many more ongoing) that have evaluated whether pessary is a beneficial strategy for preterm birth prevention in a variety of

* The Members of the FIGO Working Group for Preterm Birth, 2018–2021 are listed at the end of the article.

different populations (e.g. women with a singleton pregnancy and short cervix, twins and a short cervix, or twins regardless of cervical length). These trials have yielded inconsistent results even among women with similar risk factors for preterm birth. Some showed benefit among those who received a pessary, and others showed statistically similar results regardless of whether a pessary was used.[1,2]

2 | CLINICAL SCENARIOS

2.1 | Women with a singleton pregnancy and short cervical length

As two examples of conflicting studies among women with singleton pregnancies and a short cervix, Goya et al. randomized those with a singleton pregnancy and a cervix ≤25 mm to an Arabin pessary vs no pessary, and found that those who received the pessary had an 82% reduction in the relative risk of spontaneous preterm birth and an 86% reduction in a composite of perinatal morbidity.[1] In contrast, Nicolaides et al.[2] used a similar study design (although added progesterone if the cervix was ≤15 mm), and found no difference in either outcome.[2] Other investigations have produced similarly inconsistent findings.[3,4]

Recommendation: *In women with a singleton pregnancy and a short cervical length, a pessary should not be used in routine clinical care to reduce the frequency of preterm birth or to improve outcomes (e.g. neonatal outcomes) related to preterm birth*.

2.2 | Women with a twin pregnancy

Among a general population of women with twins, Liem et al.[5] found no difference in gestation length between women randomized to receive a pessary or no pessary. In the study by Liem et al., the population was further stratified by several subgroups of cervical length, and in the subset with a cervical length <38 mm, those with a pessary had a significantly longer gestation and better perinatal outcomes. Dang et al. used this information to design a trial in which those with twins and a cervical length <38 mm were randomized to pessary or vaginal progesterone. There was no significant difference in the frequency of preterm birth <34 weeks (16% vs 22%; RR 0.73; 95% CI 0.46–1.18), which was the primary outcome in that study. The authors did find that some secondary outcomes (e.g. composite perinatal adverse outcomes) were significantly less frequent (albeit without adjustment for multiple comparisons) among women who received the pessary.[6] Goya et al.[7] showed a considerably lower chance of spontaneous preterm birth <34 weeks (RR 0.41; 95% CI 0.22–0.76) among those with twins and a cervical length ≤25 mm who were randomized to pessary, while Nicolaides et al.—who randomized women with twins regardless of cervical length—did not find any effect, even in women with a short cervical length.[7,8] Norman et al.[9] randomly assigned 503 women with a twin pregnancy and cervical length ≤35 mm to pessary in addition to standard care or standard care alone. There was no difference in the primary obstetric outcome of spontaneous preterm birth before 34^{+0} weeks (adjusted odds ratio 0.87; 95% CI 0.55–1.38). Other investigators similarly have shown no difference in preterm birth rates among women with twins who received a pessary. However, some of these trials were smaller, with a corresponding greater chance of type II error.[10] A meta-analysis performed by Norman et al.,[9] which included their own and other published data, showed that the use of cervical pessary did not result in a statistically significant reduction in preterm birth before 34 weeks in women with a short cervix (OR 0.74; 95% CI 0.50–1.11).

Recommendation: *In women with a twin pregnancy—regardless of cervical length—pessaries should not be used in routine clinical care to reduce the frequency of preterm birth or to improve outcomes (e.g. neonatal outcomes) related to preterm birth*.

3 | CONCLUSION

While some studies have shown benefits from pessary, those benefits have often not been related to the a priori primary outcome or have been seen only after subgroup analysis in women with different cervical lengths. Other studies have shown statistically similar effects among women at risk of preterm birth regardless of whether they received a pessary. In some cases, the size of the trial has been small enough, and the confidence interval around the point estimate of the effect size sufficiently wide, that a clinically significant benefit remains possible. Interpretation of the results is further complicated because studies have varied concerning management among those enrolled, including whether or not vaginal progesterone was used. This inconsistency in findings and lack of clear delineation of a specific group of individuals among whom pessary is efficacious is the basis upon which to conclude that, at this time, there is not sufficient evidence to suggest that pessary should be used as a standard treatment to prevent preterm birth, and that its use should be reserved for study populations.

CONFLICTS OF INTEREST

William A. Grobman 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. Bo Jacobbson 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 expendidures reimbused 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 Jacobbson 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.

AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. WAG wrote the first version of the manuscript. JN and BJ revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version.

MEMBERS OF THE FIGO WORKING GROUP FOR PRETERM BIRTH, 2018–2021

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SPECIAL ARTICLE

FIGO good practice recommendations on reduction of preterm birth in pregnancies conceived by assisted reproductive technologies

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Abstract

FIGO (the International Federation of Gynecology and Obstetrics) supports assisted reproductive technologies (ART) to achieve pregnancy and supports their availability in all nations. However, the increased frequency of preterm birth must be taken into account. Therefore, before in vitro fertilization (IVF) is started, other approaches, including expectant management, should be considered. Single embryo transfer is the best approach to ensure a live, healthy child. However, increased risks for preterm birth are also associated with a singleton IVF pregnancy and should be discussed and contrasted with spontaneous conception. Increased preterm birth and other adverse pregnancy outcomes in singleton IVF cycles warrant investigations to elucidate and mitigate. Minimizing embryo manipulation during cell culture is recommended. Increased risk of preterm birth and other pregnancy complications in ART could reflect the underlying reasons for infertility. This information should be discussed and further explored.

KEYWORDS
assisted reproductive technology, child outcome, preterm delivery, single embryo transfer

*The Members of the FIGO Working Group for Preterm Birth, 2018–2021, are listed at the end of the article.

1 | INTRODUCTION

Assisted reproductive technology (ART) is an essential component of infertility treatment. FIGO (the International Federation of Gynecology and Obstetrics) supports WHO in considering childbearing a human right that should be accessible in all nations. The social stigma of childlessness can lead to isolation and abandonment of women.[1] ART accounts for approximately 1%–2% of all pregnancies globally and as much as 7% in certain countries.[2] However, ART is also a significant risk factor for preterm birth, both in high-income and low–middle-income countries, and even in situations where single embryo transfer (SET) is applied.[3,4]

Recommendation: *FIGO supports ART to achieve pregnancy and supports its availability in all nations. However, the increased frequency of preterm birth and other pregnancy complications must be considered when starting ART.*

2 | TARGETED USE OF ASSISTED REPRODUCTIVE TECHNOLOGY

In vitro fertilization (IVF) should only be used if it is indispensable, i.e., if spontaneous conception or conception using less invasive methods have failed. This can be the case in infertile couples or individuals with diagnoses such as blocked tubes or severe male infertility that rule out spontaneous fertility chances. Otherwise, a prognosis for spontaneous conception could help.[5] In case of good prognosis, there might be benefit from expectant management or less invasive treatments with tubal flushing or intra-uterine insemination. Lifestyle interventions should also be considered for appropriate women. For example, in women with anovulation due to polycystic ovary syndrome, ovulation induction can be the first-line treatment. There are also other indications for IVF that are not covered in this document.

Recommendation: Before IVF is started, other approaches, including expectant management and other less invasive treatments, should be considered.

3 | SINGLE EMBRYO TRANSFER IN ASSISTED REPRODUCTIVE TECHNOLOGY

The US Centers for Disease Control and Prevention (CDC) states that double embryo transfer in ART results in a 27%–33% twin rate, whereas SET results in a 1% twin rate.[5,6] In addition, transferring multiple embryos is unequivocally correlated with preterm birth.[4,6] This strategy has long been advocated but has not been pursued rigorously. Given that ART is increasingly performed worldwide, increased rates of twins will continue unless SET is widely utilized. We realize the global differences, but there should never be a standard procedure to transfer multiple embryos.

Recommendation: *In treatment with IVF, single embryo transfer is the best approach to prevent multiple pregnancies and subsequent preterm birth, thus maximizing the chance of having a healthy live child.*

4 | PREGNANCY COMPLICATIONS IN ART

Less appreciated than in multiple gestation pregnancies is that singleton IVF pregnancies are also associated with increased preterm birth (two-fold), stillbirths, and intrauterine growth restriction. In addition, neonatal Intensive Care Unit (NICU) admissions are also increased.[7]

Meta-analyses of singleton IVF pregnancies have shown up to 10.9% preterm birth rates (<37 weeks of gestation) versus 6.4% in a comparison group delivered at full term.[8] Thus, singleton IVF pregnancy remains a risk factor for early preterm birth even after adjustment for other risk factors such as maternal age, smoking, or prior surgical procedures for cervical intraepithelial neoplasia or infertility.[8,9] Similarly, infertility or subfertility without ART is associated with increased adverse pregnancy outcomes compared with spontaneous pregnancies.[1] Association of ART with preterm birth is also evident from conception with intrauterine insemination or ovulation induction, as singleton pregnancies resuting from these treatments do not have increased preterm birth rates.[3]

Recommendation: Increased risks for preterm birth are associated with singleton IVF. This information should be discussed and contrasted with spontaneous conception.

The increased risk for preterm birth in singleton IVF pregnancies may reflect embryo manipulation inherent in successful ART. Embryo culture, freezing/thawing procedures and endometrial transfer itself may impair implantation or the ability to maintain a pregnancy and influence the neonatal outcome.[10] Significant differences in preterm birth rates and other adverse pregnancy outcomes are observed when comparing different culture media or fresh and frozen transfer, perhaps leading to abnormal placentation.[9,11] Abnormalities of placental function as an explanation are suggested by increased maternal β-hCG and decreased pregnancy-associated plasma during early pregnancy.[12,13]

Recommendation: *Increased preterm birth and other adverse pregnancy outcomes in singleton IVF cycles warrant investigations to elucidate and mitigate. Therefore, minimizing embryo manipulation during cell culture is recommended.*

An alternative explanation for increased preterm birth and other adverse outcomes in singleton IVF cycles is that these outcomes could reflect the underlying reason why ART infertility was required to achieve a pregnancy. By analogy, birth defects are increased 30% (odds ratio 1.3) in offspring conceived using IVF or intra-cytoplasmic sperm injection (ICSI).[14,15] Moreover, birth defects are increased by 20% in subfertile women whose time to conceive is delayed (>1 year) but who never required IVF or ICSI.[16]

Recommendation: Increased risks for preterm birth and other pregnancy complications in ART could reflect the underlying reasons for infertility. This information should be discussed.

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AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept of the paper. KM wrote the first version of the manuscript. BWM, BJ, and WAG revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version of the manuscript.

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SPECIAL ARTICLE

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FIGO good practice recommendations on delayed umbilical cord clamping

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Abstract

Delayed cord clamping in the first minute in preterm infants born before 34 weeks of gestation improves neonatal hematologic measures and may reduce mortality without increasing any other morbidity. In term-born babies, it also seems to improve both the short- and long-term outcomes and shows favorable scores in fine motor and social domains. However, there is insufficient evidence to show what duration of delay is best. The current evidence supports not clamping the cord before 30 seconds for preterm births. Future trials could compare different lengths of delay. Until then, a period of 30 seconds to 3 minutes seems justified for term-born babies.

KEYWORDS
delayed cord clamping, neonatal outcomes, preterm delivery, term delivery

1 | INTRODUCTION

Since active management of the third stage of labor was introduced, early clamping of the umbilical cord has spread across the world. However, during the last decade, clinical insights have questioned this policy. This gained support through extensive clinical trials showing that late cord clamping results in better neonatal outcomes in preterm and term-born babies.[1,2] Delayed cord clamping allows blood flow between the placenta and baby to continue during the third stage of labor, leading to a more stable neonatal hemodynamic transition.[3] In addition, as part of the neonate's physiological transition naturally occurring during the third stage of labor there is a progressive increase in heart rate, which is now considered the most reliable indicator of normalcy. In this sense, delayed cord clamping provides a safe time lapse to avoid rushing to perform unnecessary interventions.[4]

* The Members of the FIGO Working Group for Preterm Birth, 2018–2021 are listed at the end of the article.

A recent study by Katheria et al.[5] found that in preterm infants born before 32 weeks of gestation more than 90% of infants established respirations with colorimetric carbon dioxide change within the first minute after birth when they received stimulation. This is important for cardiovascular stability to occur; the newborn must be breathing, therefore during delayed cord clamping attempts should be made to get them to breathe spontaneously. This, as a minimum, should be conducted with stimulation and should allow a safe time to assess the slow initiation of spontaneous breathing and to provide minimally invasive medical support, if needed, avoiding unnecessary and potentially harmful interventions.

The shorter the gestational age, the more significant the delay in initiating effective breathing owing to an immature respiratory drive, poor muscle strength, and surfactant deficiency. The initial functional residual lung capacity provides an insignificant amount of pulmonary exchange during the first breaths. Safety of respiration may depend transiently on the placental gas exchange that makes a substantial contribution to the infant's oxygen needs during these seconds and minutes of transition.

Caring for the preterm infant with an intact umbilical cord and in the "maternal space" allows a safe time for assessing the slow initiation of spontaneous breathing.

2 | CLINICAL SCENARIOS

2.1 | Delayed cord clamping at preterm birth

Systematic reviews provide moderate-quality evidence that delayed cord clamping in the first minute in preterm infants born before 34 weeks of gestation improves neonatal hematologic measures and may reduce mortality without increasing any other morbidity.[6]

Delayed clamping reduced hospital mortality (risk ratio [RR] 0.68; 95% CI 0.52–0.90; risk difference −0.03; 95% CI −0.05 to −0.01; $P = 0.005$; number needed to benefit 33; 95% CI 20–100).[7] In three trials including 996 infants at or before 28 weeks of gestation, delayed cord clamping reduced hospital mortality (RR 0.70; 95% CI 0.51–0.95; risk difference −0.05; 95% CI −0.09 to −0.01; $P = 0.02$; number needed to benefit 20; 95% CI 11–100).[7] Delayed clamping reduced the incidence of a low Apgar score at 1 minute, but not at 5 minutes, and did not reduce the incidence of intubation for resuscitation, admission temperature, mechanical ventilation, intraventricular hemorrhage, brain injury, chronic lung disease, patent ductus arteriosus, necrotizing enterocolitis, late-onset sepsis, or retinopathy of prematurity.[7]

2.2 | Delayed cord clamping at term birth

Although not the focus of these recommendations, there is also evidence that expectant management in full-term babies is beneficial in the third stage of labor in the short and long term.[8] In the short term, delayed cord clamping increases early hemoglobin concentrations and iron stores in infants.[8] In the long term, delayed cord clamping is likely to be beneficial as long as access to treatment for jaundice requiring phototherapy is available.

A randomized trial of full-term infants from low-risk pregnancies in a high-income country assessed neurodevelopment at 4 years and compared delayed versus early cord clamping. Favorable scores for delayed cord clamping were found in the fine motor and social domains at 4 years of age, especially in boys.[2] Prevention of iron deficiency in infancy may promote neurodevelopment. Delayed umbilical cord clamping prevents iron deficiency at 4–6 months of age, and long-term effects have yet to be reported.[8] Some trials have also followed the impact of cord clamping on the early developing brain at 12 months in a healthy population, concluding that infants who received delayed cord clamping had greater myelin content in brain regions involving motor, function, visual, spatial, and sensory processing.[9]

3 | RECOMMENDATIONS

Delayed cord clamping in the first minute in preterm infants born before 34 weeks of gestation improves neonatal hematologic measures and may reduce mortality without increasing any other morbidity. In term-born babies, it also seems to improve the short- and long-term outcomes and showed favorable scores in the fine motor and social domains at 4 years of age.

However, there is insufficient evidence to show what duration of delay is best. The current evidence supports not clamping the cord before 30 seconds for preterm births. Future trials could compare different lengths of delay. Until then, at term a period of 30 seconds to 3 minutes seems justified or until the cord is collapsed and white.

For both preterm and term-born babies, during the cord clamping delay, attempts should be made to get them to breathe spontaneously. Additional research is needed to examine the long-term child outcome related to the timing of umbilical cord clamping and the developing brain.

CONFLICTS OF INTEREST

Ana Bianchi 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 Jacobbson 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 such as NNFM 2015, ESPBC 2016, and a Nordic educational meeting about NIPT and pre-eclampsia screening. Bo Jacobbson is also Chair of the FIGO Working Group for Preterm

Birth and the European Association of Perinatal Medicine special interest group on 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.

AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept for the paper. BWM and AB wrote the first version and BJ revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version.

MEMBERS OF THE FIGO WORKING GROUP FOR PRETERM BIRTH, 2018–2021

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SPECIAL ARTICLE

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FIGO good practice recommendations on progestogens for prevention of preterm delivery

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Abstract

Women at high risk of preterm birth (either a previous spontaneous preterm birth and/or sonographic short cervix) with a singleton gestation should be offered daily vaginal progesterone or weekly 17-OHPC treatment to prevent preterm birth. Benefit is most significant in those with prior history of preterm birth and a short cervix. For women with a previous spontaneous preterm birth and a cervix ≥30 mm the effectiveness of progesterone is uncertain. In asymptomatic women with no prior history of previous preterm birth, no mid-trimester loss, or no short cervical length, progesterone therapy is not recommended for the prevention of preterm birth. For those with unselected multiple pregnancies, progesterone therapy is not recommended for the prevention of preterm birth. Daily vaginal progesterone or weekly 17-OHPC treatment can be used for the prevention of preterm birth. The preparation used should be decided by the woman and her clinician. There is no evidence of neurological or developmental benefit or harm in babies whose mothers use progestogens for preterm birth prevention antenatally.

KEYWORDS
antenatal, child outcome, preterm delivery, prevention, progesterone

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1 | INTRODUCTION

Endogenous progesterone is essential for the maintenance of pregnancy, and local decline in progesterone activity is thought to have a role in labor induction. Therefore, progestogens have been increasingly used in women at high risk of preterm birth as they are believed to counter this functional decline and provide anti-inflammatory effects. Several randomized controlled trials (RCTs) and meta-analyses have been undertaken to help provide an evidence-based approach to prevent preterm birth and determine the optimal regimes and populations to target.

Types of progestogens:

1. Natural progesterone, similar to that produced by the body and commonly administered as a vaginal gel or pessary
2. Semisynthetic progestogens, which have a different chemical structure and include 17-hydroxyprogesterone caproate (17-OHPC), given as a weekly intramuscular injection.

2 | ASYMPTOMATIC WOMEN WITH A SINGLETON GESTATION AT HIGH RISK OF PRETERM BIRTH

The EPPPIC meta-analysis included individual patient data from randomized trials of progestogens to prevent preterm birth, including 31 trials and 11 644 participants.[1] It demonstrated that both vaginal progesterone and 17-OHPC reduced the risk of preterm birth before 34 weeks for a high-risk population with singleton gestations. In addition, a benefit was seen among included participants who were only eligible for the original trials due to short cervical length (defined by different thresholds in different trials) or history of preterm birth (vaginal progesterone: 9 trials, 3769 women; relative risk [RR] 0.78, 95% CI 0.68–0.90; 17-OHPC: 5 trials, 3053 women; RR 0.83, 95% CI 0.68–1.01).

Recommendation: Women at high risk of preterm birth (either a previous spontaneous preterm birth and/or sonographic short cervix) with a singleton gestation should be offered daily vaginal progesterone or weekly 17-OHPC treatment to prevent preterm birth. Whether progesterone is effective in women with previous spontaneous preterm birth and a normal length cervix (>30 mm at midtrimester ultrasound) is uncertain.

3 | ASYMPTOMATIC WOMEN WITH A SINGLETON GESTATION WITHOUT A PRIOR HISTORY OF PRETERM BIRTH OR SHORT CERVICAL LENGTH

In the EPPPIC meta-analysis, the effect of progestogens on preterm birth reduction did not statistically differ based on the history of preterm birth or the presence of a short cervix. However, few women enrolled in any of the included trials that did not have either of these risk factors. As such, it remains uncertain whether and to what extent progestogens will or will not benefit this population.

Recommendation: In asymptomatic women with no prior history of previous preterm birth, no mid-trimester loss, or no short cervical length, progesterone therapy is not recommended for the prevention of preterm birth.

4 | ASYMPTOMATIC WOMEN WITH A MULTIPLE PREGNANCY

The EPPPIC meta-analysis shows that progestogen administration does not reduce preterm birth before 34 weeks in women with unselected multiple pregnancies (16 trials; vaginal progesterone: RR 1.01, 95% CI 0.84–1.20; 17-OHPC: RR 1.04, 95% CI 0.92–1.18).[1] The majority of women included in the meta-analysis had no other risk factors for preterm birth. This is consistent with the 2019 Cochrane review, which included 16 trials and 4548 women.[2] A recent additional study came to the same conclusion for unselected multiple pregnancies.[3]

Recommendation: For women with unselected multiple pregnancies, progesterone therapy is not recommended for the prevention of preterm birth. For women with multiple pregnancies and a risk factor such as previous preterm birth, it is unknown whether progesterone therapy is effective.

5 | OTHER ISSUES

5.1 | Type of progestogen

In the EPPPIC meta-analysis, there were only two trials that provided direct data comparing vaginal progesterone and 17-OHPC, and these showed no statistical difference between the two types of progestogen (preterm birth <34 weeks RR 1.18, 95% CI 0.69–2.03).[1]

Recommendation: Daily vaginal progesterone or weekly 17-OHPC treatment can be used for the prevention of preterm birth. The preparation used should be decided by the woman and her clinician.

5.2 | Long-term effects of progestogens

Only two studies have examined the long-term effects of progestogens in those with singleton gestations.[4,5] The follow-up study to the Meis et al. 2003 trial of 17-OHPC showed no difference between 17-OHPC and placebo groups in any of the developmental domains of children assessed at approximately two years.[4] A childhood developmental assessment was one of the three primary outcomes in the OPPTIMUM study, which showed no difference in cognitive composite score between the active and the placebo groups.[5] A recent systematic review comprising a

multitude of developmental measurements with a broad age range at assessment did not find evidence of benefit or harm in offspring prenatally exposed to progesterone treatment for the prevention of preterm birth (5 trials, 4222 measurements of children between 6 months and 8 years).[6]

Recommendation: There is no evidence of neurological or developmental benefit or harm in babies whose mothers use progestogens for preterm birth prevention antenatally.

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. Natalie Suff reports no conflicts of interest. Jo 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. Bo Jacobbson 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 expendidures reimbused 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 Jacobbson 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. Ben W. Mol reports an investigator grant from NHMRC; consultancy for ObsEva; and research funding from Guerbet, Ferring, and Merck KGaA. William A. Grobman reports no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. AS wrote the first version of the manuscript. JLS, BJ, BM, and WAG revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version.

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