

## SPECIAL ARTICLE

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

Ben W. Mol<sup>1,2</sup> | Bo Jacobsson<sup>3,4,5</sup> | William A. Grobman<sup>6</sup> | Kelle Moley<sup>7</sup> |  
the FIGO Working Group for Preterm Birth\*

<sup>1</sup>Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia

<sup>2</sup>Aberdeen Centre for Women's Health Research, Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, UK

<sup>3</sup>Department of Obstetrics and Gynecology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

<sup>4</sup>Department of Obstetrics and Gynecology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden

<sup>5</sup>Department of Genetics and Bioinformatics, Domain of Health Data and Digitalization, Institute of Public Health, Oslo, Norway

<sup>6</sup>Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

<sup>7</sup>Bill and Melinda Gates Foundation, Seattle, Washington, USA

## Correspondence

Ben W. Mol, Department of Obstetrics and Gynaecology, Faculty of Medicine, Nursing and Health Sciences, Block F, level 5, Monash Medical Centre, 246 Clayton Road, Clayton, Vic. 3168, Australia.  
Email: ben.mol@monash.edu

## Funding information

This work has been supported by grants from March of Dimes to the FIGO Working Group for Preterm Birth.

## 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.

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## 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 child-bearing a human right that should be accessible in all nations. The social stigma of childlessness can lead to isolation and abandonment of women.<sup>1</sup> ART accounts for approximately 1%–2% of all pregnancies globally and as much as 7% in certain countries.<sup>2</sup> 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.<sup>3,4</sup>

*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.<sup>5</sup> 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.<sup>5,6</sup> In addition, transferring multiple embryos is unequivocally correlated with preterm birth.<sup>4,6</sup> 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.<sup>7</sup>

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.<sup>8</sup> 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.<sup>8,9</sup> Similarly, infertility or subfertility without ART is associated with increased adverse pregnancy outcomes compared with spontaneous pregnancies.<sup>1</sup> Association of ART with preterm birth is also evident from conception with intrauterine insemination or ovulation induction, as singleton pregnancies resulting from these treatments do not have increased preterm birth rates.<sup>3</sup>

*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.<sup>10</sup> 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.<sup>9,11</sup> Abnormalities of placental function as an explanation are suggested by increased maternal  $\beta$ -hCG and decreased pregnancy-associated plasma during early pregnancy.<sup>12,13</sup>

*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).<sup>14,15</sup> 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.<sup>16</sup>

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

### ACKNOWLEDGEMENT

This document is endorsed by FIGO Committee for Reproductive Medicine, Endocrinology and Infertility, and was discussed at their committee meeting on March 11, 2021.

## CONFLICTS OF INTEREST

Ben W. Mol reports an investigator grant from NHMRC; consultancy for ObsEva; and research funding from Guerbet, Ferring, and Merck KGaA. Bo Jacobsson reports Research grants from Swedish Research Council, Norwegian Research Council, March of Dimes, Burroughs Wellcome Fund and the US National Institute of Health; clinical diagnostic trials on NIPT with Ariosa (completed), Natera (ongoing), Vanadis (completed) and Hologic (ongoing) with expenditures reimbursed per patient; clinical probiotic studies with product provided by FukoPharma (ongoing, no funding) and BioGaia (ongoing; also provided a research grant for the specific study); collaboration in IMPACT study where Roche, Perkin Elmer and Thermo Fisher provided reagents to PLGF analyses; coordination of scientific conferences and meetings with commercial partners as such as NNFM 2015, ESPBC 2016 and a Nordic educational meeting about NIPT and preeclampsia screening. Bo Jacobsson is also Chair of the FIGO Working Group for Preterm Birth and the European Association of Perinatal Medicine's special interest group of preterm delivery; steering group member of Genomic Medicine Sweden; chairs the Genomic Medicine Sweden complex diseases group; and is Swedish representative in the Nordic Society of Precision Medicine. William Grobman and Kelle Moley report no conflicts of interest.

## 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.

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

Bo Jacobsson (Chair), Joe Leigh Simpson, Jane Norman, William Grobman, Ana Bianchi, Stephen Munjanja, Catalina María Valencia González, Ben W. Mol, Andrew Shennan.

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**How to cite this article:** Mol BW, Jacobsson B, Grobman WA, Moley K; the FIGO Working Group for Preterm Birth. FIGO good practice recommendations on reduction of preterm birth in pregnancies conceived by assisted reproductive technologies. *Int J Gynecol Obstet*. 2021;155:13-15. <https://doi.org/10.1002/ijgo.13834>