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Society for Maternal-Fetal Medicine Consult Series #60: Management of pregnancies resulting from in vitro fertilization

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The use of assisted reproductive technology has increased in the United States in the past several decades. Although most of these pregnancies are uncomplicated, in vitro fertilization is associated with an increased risk for adverse perinatal outcomes primarily caused by the increased risks of prematurity and low birthweight associated with in vitro fertilization pregnancies. This Consult discusses the management of pregnancies achieved with in vitro fertilization and provides recommendations based on the available evidence. The recommendations by the Society for Maternal-Fetal Medicine are as follows: (1) we suggest that genetic counseling be offered to all patients undergoing or who have undergone in vitro fertilization with or without intracytoplasmic sperm injection (GRADE 2C); (2) regardless of whether preimplantation genetic testing has been performed, we recommend that all patients who have achieved pregnancy with in vitro fertilization be offered the options of prenatal genetic screening and diagnostic testing via chorionic villus sampling or amniocentesis (GRADE 1C); (3) we recommend that the accuracy of first-trimester screening tests, including cell-free DNA for aneuploidy, be discussed with patients undergoing or who have undergone in vitro fertilization (GRADE 1A); (4) when multifetal pregnancies do occur, we recommend that counseling be offered regarding the option of multifetal pregnancy reduction (GRADE 1C); (5) we recommend that a detailed obstetrical ultrasound examination (CPT 76811) be performed for pregnancies achieved with in vitro fertilization and intracytoplasmic sperm injection (GRADE 1B); (6) we suggest that fetal echocardiography be offered to patients with pregnancies achieved with in vitro fertilization and intracytoplasmic sperm injection (GRADE 2C); (7) we recommend that a careful examination of the placental location, placental shape, and cord insertion site be performed at the time of the detailed fetal anatomy ultrasound, including evaluation for vasa previa (GRADE 1B); (8) although visualization of the cervix at the 18 0/7 to 22 6/7 weeks of gestation anatomy assessment with either a transabdominal or endovaginal approach is recommended, we do not recommend serial cervical length assessment as a routine practice for pregnancies achieved with in vitro fertilization (GRADE 1C); (9) we suggest that an assessment of fetal growth be performed in the third trimester for pregnancies achieved with in vitro fertilization; however, serial growth ultrasounds are not recommended for the sole indication of in vitro fertilization (GRADE 2B); (10) we do not recommend low-dose aspirin for patients with pregnancies achieved with IVF as the sole indication for preeclampsia prophylaxis; however, if 1 or more additional risk factors are present, low-dose aspirin is recommended (GRADE 1B); (11) given the increased risk for stillbirth, we suggest weekly antenatal fetal surveillance beginning by 36 0/7 weeks of gestation for pregnancies achieved with in vitro fertilization (GRADE 2C); (12) in the absence of studies focused specifically on timing of delivery for pregnancies achieved with IVF, we recommend shared decision-making between patients and healthcare providers when considering induction of labor at 39 weeks of gestation (GRADE 1C).

Key words: assisted reproductive technology, intracytoplasmic sperm injection, in vitro fertilization

Introduction

Successful in vitro fertilization (IVF) leading to a live birth was initially reported in 1978.[1] Since then, the use of assisted reproductive technology (ART) has increased steadily and now accounts for 1.6% of all infants and 18.3% of all multiple-birth infants in the United States.[2] Although most of these pregnancies are uncomplicated, IVF is associated with adverse perinatal outcomes primarily caused by the increased risks of prematurity and low birthweight associated with pregnancies achieved with IVF. Such risks are often compounded by the higher rates of twinning and

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higher-order multiples in pregnancies achieved with IVF. More recent studies and meta-analyses demonstrate that pregnancies achieved with IVF also carry a doubling in the risk for severe maternal morbidity even after controlling for maternal age, parity, and comorbid conditions.[3–8]

Factors that may contribute to the adverse effects of IVF on pregnancy outcomes include those related to the IVF procedure itself (medications, laboratory conditions during embryo culture, culture medium, cryopreservation, and thawing) and the maternal conditions associated with subfertility and infertility (including pregnancy at an older age and reduced ovarian reserve). It is often impossible to separate the individual factors affecting the risks for adverse outcomes in pregnancies achieved with IVF, making it difficult to mitigate the risks associated with IVF. This Consult discusses the management of pregnancies achieved with IVF and provides recommendations based on the available evidence.

What genetic conditions should be discussed with patients considering to undergo or who have undergone in IVF?

The IVF procedure itself does not appear to lead to a higher prevalence of chromosomal anomalies when compared with naturally occurring pregnancies.[9,10] However, several other factors may play a role in the increased risk for chromosomal anomalies in these pregnancies, including pregnancy at an older age and polycystic ovary syndrome.[11,12] Severe male and female factor infertility may be associated with a higher risk for chromosome anomalies.[13] A 1.5% rate of karyotypic anomalies is reported in couples referred for IVF (1.8% for men and 1.2% for women).[14] The need for genetic screening is well established for several infertile subpopulations, including patients with severe sperm alterations and patients presenting with primary amenorrhea, premature menopause, and recurrent pregnancy loss.[14] Among the approximately 10% of men diagnosed with oligospermia or azoospermia without physical obstruction of the vas deferens, 8% to 15% carry a microdeletion in the long arm of the Y chromosome.[15] These findings have implications when intracytoplasmic sperm injection (ICSI) is performed because chromosomal or gene defects that might normally be lost or eliminated by natural means could be transmitted to the offspring.

Other studies report a significantly increased rate of de novo chromosomal abnormalities in pregnancies achieved with ICSI compared with a reference group of naturally occurring pregnancies or the general population ($P<.001$).[16,17] In a nationwide cohort of ongoing pregnancies achieved with IVF, of those who underwent invasive testing, chromosome aberrations were more common in the ICSI-treated group than the IVF alone-treated group (1.3% vs 0.5%; $P<.001$) despite the fact that women who became pregnant after IVF alone were significantly older than those who became pregnant after IVF with ICSI ($P<.001$).[18] Similar findings have been reported by other groups.[19]

Patients with reduced ovarian reserve and primary ovarian insufficiency have an increased risk for being full mutation or premutation carriers of fragile X. These patients typically undergo *FMR1* gene testing before undergoing IVF. Preimplantation genetic testing should be offered for monogenic disorders with the transfer of only embryos carrying the normal X chromosome.[20,21]

Genomic imprinting is a phenomenon by which genes are epigenetically regulated and expressed according to parental origin. Imprinting syndromes are thought to occur more frequently in the offspring of subfertile parents,[22] including those undergoing IVF. Increased rates of Beckwith-Wiedemann syndrome (BWS),[23–26] Angelman or Prader-Willi syndrome (PWS), and Russell-Silver syndrome have been reported in case-control studies.[27,28] A more recent meta-analysis yielded estimates of specific associations between ART and Russell-Silver syndrome (odds ratio [OR], 11.3; 95% confidence interval [CI], 4.5–28.5), BWS (OR, 5.8; 95% CI, 3.1–11.1), Angelman syndrome (OR, 4.7; 95% CI, 2.6–8.5), and PWS (OR, 2.2; 95% CI, 1.6–3.0).[29] A systematic review and meta-analysis on the subject concluded that pregnancy achieved with ART, when compared with naturally occurring pregnancies, is associated with an increased risk for imprinting disorders (adjusted odds ratio [aOR], 3.67; 95% CI, 1.39–9.74).[30] However, given the low prevalence of these syndromes, the absolute risk remains very small. **We suggest that genetic counseling be offered to all patients undergoing or who have undergone IVF with or without ICSI (GRADE 2C)**.[31]

What are the different types of preimplantation genetic testing?

IVF is often accompanied by preimplantation genetic testing (PGT). There are 3 types of PGT: Preimplantation genetic testing for aneuploidy (PGT-A), preimplantation genetic testing for monogenic disorders (PGT-M), and preimplantation genetic testing for structural (chromosomal) rearrangements (PGT-SR).[32]

PGT-A focuses on the detection of de novo aneuploidies, such as the common trisomies. Because aneuploidy is a leading cause of implantation failure, miscarriage, and congenital abnormalities, PGT-A before transfer has been proposed to increase the implantation and pregnancy rates per transfer and lower miscarriage rates. Most recent techniques involve molecular testing of all chromosomes using quantitative polymerase chain reaction, microarray technology, or next-generation sequencing on several trophoectoderm cells sampled from day 5 to 6 blastocysts.

Regardless of the technique used for preimplantation genetic testing, PGT-A does not replace the recommendation for prenatal screening or diagnosis. PGT-A samples the trophoectoderm, which gives rise to the placenta, not the inner cell mass, which gives rise to the fetus. Discordant aneuploidy findings between trophoectoderm and inner cell mass are reported to be as high as 50% in discarded frozen embryos.[33] In 1 systematic review of 26 studies that

compared the initial PGT-A and reanalysis results from 1124 embryos, concordance rates were 93.8% for euploidy, 81.4% for full aneuploidy, and 42.6% for mosaic aneuploidy (all $P<.05$). The authors of the systematic review concluded that the increased discordance rates with PGT-A are likely caused by the inclusion of mosaic embryos.[34] True rates of false-negative and false-positive diagnoses for PGT-A in clinical use are not well documented; euploid embryos misdiagnosed as aneuploid are discarded, and aneuploid embryos misdiagnosed as normal often miscarry. The value of PGT-A as a screening test for IVF patients has been debated.[35–37] The Practice Committee of the American Society for Reproductive Medicine states that there is insufficient evidence to recommend the routine use of blastocyst biopsy with aneuploidy testing in all infertile patients.[38]

PGT-M is used to diagnose monogenic disorders, most commonly in couples with previous offspring affected by single-gene disorders (such as cystic fibrosis) or who have undergone carrier screening with both partners testing positive for a mutation associated with a genetic disease. Less frequent indications are a desire to select a child who is HLA-compatible with a sibling for stem cell therapy, sex selection in cases of sex-linked disorders (eg, Duchenne muscular dystrophy), or selection of embryos unaffected by late-onset autosomal dominant disorders (eg, Huntington disease) in the presence of a positive family history.

PGT-SR is used to diagnose structural chromosomal rearrangements. In such cases, one partner is usually known to be a carrier of a balanced translocation or a deletion or duplication. The goal of both PGT-M and PGT-SR is to allow the transfer of an unaffected embryo. For both PGT-M and PGT-SR, it is recommended that a confirmatory diagnostic test be offered during the pregnancy.[39] This recommendation reflects the inherent difficulties of testing the limited number of cells obtained from blastocyst biopsy and the known biologic and human factors that may lead to misdiagnosis. Misdiagnoses can be caused by unprotected sexual intercourse during the IVF cycle, human error (transfer of a wrong embryo), or postzygotic mitotic changes. False-negative diagnoses may be caused by contaminating extraneous DNA, allele drop-out, or partial amplification and may lead to the transfer of abnormal embryos. Despite these limitations, reported misdiagnosis rates are <1 in 200 pregnancies following PGT-M.[40] Many patients, however, do not wish to pursue invasive testing after PGT. **Regardless of whether PGT has been performed, we recommend that all patients who have achieved pregnancy with IVF be offered the options of prenatal genetic screening and diagnostic testing via chorionic villus sampling or amniocentesis (GRADE 1C).**

Furthermore, embryo mosaicism is present in an estimated 16% to 21% of blastocysts.[41] If euploid embryos are unavailable, aneuploid mosaic embryos are sometimes transferred, because a mosaic embryo can develop into a healthy euploid fetus.[42] The probability of confirmation of the aneuploidy on amniocytes is reported to average 11.4%; however, probability depends on the chromosome involved in the aneuploidy, with rates of 45% for trisomy 21, 22% for trisomy 18, 2% for trisomy 13, 5% for trisomy 16, 12% for trisomy 14, and 5% for trisomy 20.[43] For chromosomes with imprinted genes (6, 7, 11, 14, and 15), the risk for clinically meaningful uniparental disomy via trisomy or monosomy rescue mechanisms averages about 5%.[43] Prenatal diagnostic testing should be offered to patients with pregnancies that are achieved by the transfer of an embryo with a mosaic trisomy or monosomy. Consultation with a genetic counselor or geneticist can be offered to discuss diagnostic testing for these patients. Screening with cell-free DNA (cfDNA) has limited clinical utility given that it tests DNA of placental (not fetal) origin, leading to unknown performance for low-level mosaicism and unclear positive predictive values in this clinical setting.[44]

What is the accuracy of first-trimester genetic screening tests in pregnancies achieved with in vitro fertilization?

The accuracy of first-trimester genetic screening tests for aneuploidies may be affected by IVF. In a recent systematic review, when compared with naturally occurring pregnancies, pregnancies achieved with IVF were associated with decreased pregnancy-associated plasma protein A (PAPP-A) and increased nuchal translucency (NT) measurements in the first trimester and decreased alpha fetoprotein and transcription factor μE3 and increased total hCG in the second trimester.[45] Another meta-analysis confirmed the significantly lower PAPP-A levels in any IVF (with or without ICSI) vs controls (RR, 0.85; 95% CI 0.80–0.90), IVF vs controls (RR, 0.82; 95% CI, 0.74–0.89), and ICSI vs controls (RR, 0.83, 95% CI, 0.79–0.86) but did not find a difference in NT measurements.[46] These findings suggest a potential increased risk for false-positive results for aneuploidies in patients who undergo first-trimester combined screening.[47]

Studies using cfDNA report a lower fetal fraction (FF) in pregnancies achieved with IVF, perhaps reflecting smaller placental mass.[48] This lower FF leads to higher rates of failed cfDNA results compared with naturally occurring pregnancies (5.2% vs 2.2%; $P<.001$).[49] However, IVF does not appear to be a risk factor for failed results on repeat cfDNA testing (second draw), which has an overall success rate of about 53% on repeat draw.[50] **We recommend that the accuracy of first-trimester screening tests, including cfDNA for aneuploidy, be discussed with patients undergoing or who have undergone IVF (GRADE 1A).**

Does multifetal pregnancy reduction reduce the risks associated with multiple gestations?

Given the increase in maternal and perinatal morbidity and mortality associated with twins and higher-order multifetal pregnancies,[51] efforts should be made to limit multifetal pregnancies during the course of ART. However, even when a single embryo is transferred, the risk of monozygotic twins

is increased, often associated with extended culture. The odds of a monozygotic twin pregnancy after transfer at the blastocyst stage compared with the cleavage stage is 2.18 (95% CI, 1.93–2.48).[52]

When multifetal pregnancies do occur, we recommend that counseling be offered regarding the option of multifetal pregnancy reduction (GRADE 1C).[53] Multifetal pregnancy reduction has been shown to reduce the risks of preterm birth, neonatal morbidity, and maternal complications.[52,53] The framework provided in the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion No. 719: Multifetal Pregnancy Reduction, may be useful for counseling patients.

Are congenital anomalies increased in pregnancies achieved with in vitro fertilization?

Meta-analyses demonstrate that there are associations between IVF with or without ICSI and congenital malformations, although it remains unclear if this association is because of infertility, factors associated with the procedure, or both.[54–56] It is also difficult to distinguish the risk associated with IVF alone vs IVF with ICSI. Pooled estimates of total major congenital malformations per 10,000 births are 475.8 (95% CI, 304.9–735.2) among singleton pregnancies achieved with IVF with or without ICSI vs 317.6 (95% CI, 145.2–680.8) among naturally occurring pregnancies with an absolute difference of 158.2 per 10,000 births.[54] Not all organ systems are equally affected. Pooled estimates for specific malformations as derived from a meta-analysis are displayed in the Table.[54]

Similar increases in fetal anomalies are reported for pregnancies achieved with ICSI in national registries.[57,58] Therefore, **we recommend that a detailed obstetrical ultrasound examination (CPT 76811) be performed for pregnancies achieved with IVF and ICSI (GRADE 1B).**[59]

In addition, a systematic review reported higher rates of total congenital heart disease (CHD) in the IVF with or without ICSI population than among naturally occurring pregnancies (1.30% vs 0.68%).[60] Similar findings are observed in other studies, which report the highest risk for cardiac anomalies to be associated with ICSI (aOR, 3.0; 95% CI, 1.0–8.9).[61] The effect appears to be caused, at least in part, by subfertility.[62] However, a recent prospective cohort study reported that the incidence of CHD in pregnancies achieved with IVF without other risk factors is not significantly different from baseline population rates (OR, 1.4; 95% CI, 0.9–2.1), although these findings were based on data from a single academic medical center, limiting the generalizability.[63] The cost-effectiveness of routine screening for CHD in pregnancies following IVF has also been questioned.[63,64] It is important to note that in this recent study by Chung et al[64], universal fetal echocardiography in pregnancies achieved by IVF was associated with a higher detection rate of CHDs than with screening only when abnormal cardiac findings were noted on a detailed anatomy scan. Therefore, **we suggest that fetal echocardiography be offered to patients with pregnancies achieved with IVF and ICSI (GRADE 2C).**[65]

TABLE

Pooled estimates of rates (per 1000) for specific congenital anomalies in singleton pregnancies following in vitro fertilization, with or without intracytoplasmic sperm injection compared with naturally occurring pregnancies (95% confidence interval)

Organ system	IVF with or without ICSI pregnancies	Naturally occurring pregnancies
Cleft lip or palate	1.3 (0.9–1.7)	1.2 (1.0–1.6)
Eye, ear, face, neck	1.7 (0.8–3.6)	1.5 (0.8–2.8)
CNS	1.7 (1.2–2.4)	1.7 (1.2–2.6)
Respiratory system	0.8 (0.4–1.6)	0.8 (0.5–1.4)
GI	3.8 (2.4–6.0)	2.5 (1.4–4.5)
Musculoskeletal	11.0 (6.7–18.1)	8.1 (4.7–13.6)
Urogenital	10.9 (6.9–17.2)	6.4 (4.5–9.1)
Cardiovascular	5.7 (5.3–11.2)	5.2 (4.5–9.1)

Data from Chen et al.[54]

CI, confidence interval; *CNS*, central nervous system; *GI*, gastrointestinal; *ICSI*, intracytoplasmic sperm injection; *IVF*, in vitro fertilization.

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Are placental anomalies increased in pregnancies achieved with in vitro fertilization?

Several placental implantation disorders are more common with IVF.[66] Pregnancies achieved with IVF are associated with higher risks for abnormal placental shape (bilobed placenta, accessory placental lobes) compared with naturally occurring pregnancies.[67,68] Pregnancies achieved by ART have higher odds of placenta previa (OR, 2.72; 95% CI, 2.04–3.40 in singleton pregnancies) when compared with naturally occurring pregnancies.[69] The risk of placenta previa may be even higher for pregnancies achieved after blastocyst transfer than for pregnancies achieved after cleavage-stage transfer (aOR, 2.18; 95% CI, 1.79–2.65) and naturally occurring pregnancies (aOR, 6.38; 95% CI, 5.31–7.66).[70]

Singleton pregnancies achieved with IVF have higher rates of marginal or velamentous cord insertion than naturally occurring singletons.[71] A systematic review and meta-analysis of 13 studies (2 prospective cohort studies, 10 retrospective cohort studies, and 1 case-control study) reporting on 569,410 patients with 325 cases of vasa previa found that pregnancies achieved with IVF are at increased risk for vasa previa (OR, 19; 95% CI, 6.6–54).[71,72] However, it is unclear whether such risk is independent of the

Summary of recommendations

Number	Recommendations	GRADE
1	We suggest that genetic counseling be offered to all patients undergoing or who have undergone IVF, with or without ICSI.	2C
2	Regardless of whether PGT has been performed, we recommend that all patients who have achieved pregnancy with IVF be offered the options of prenatal genetic screening and diagnostic testing via chorionic villus sampling or amniocentesis.	1C
3	We recommend that the accuracy of first-trimester screening tests, including cfDNA for aneuploidy, be discussed with patients undergoing or who have undergone IVF.	1A
4	When multifetal pregnancies do occur, we recommend that counseling be offered regarding the option of multifetal pregnancy reduction.	1C
5	We recommend that a detailed obstetrical ultrasound examination (CPT 76811) be performed for pregnancies achieved with IVF and ICSI.	1B
6	We suggest that fetal echocardiography be offered to patients with pregnancies achieved with IVF and ICSI.	2C
7	We recommend that a careful examination of the placental location, placental shape, and cord insertion site be performed at the time of the detailed fetal anatomy ultrasound, including evaluation for vasa previa.	1B
8	Although visualization of the cervix at the 18 0/7 to 22 6/7 weeks of gestation anatomy assessment with either a transabdominal or endovaginal approach is recommended, we do not recommend serial cervical length assessment as a routine practice for pregnancies achieved with IVF.	1C
9	We suggest that an assessment of fetal growth be performed in the third trimester for pregnancies achieved with IVF; however, serial growth ultrasounds are not recommended for the sole indication of IVF.	2B
10	We do not recommend low-dose aspirin for patients with pregnancies achieved with IVF as the sole indication for preeclampsia prophylaxis; however, if one or more additional risk factors are present, low-dose aspirin is recommended.	1B
11	Given the increased risk for stillbirth, we suggest weekly antenatal fetal surveillance beginning by 36 0/7 weeks of gestation for pregnancies achieved with IVF.	2C
12	In the absence of studies focused specifically on timing of delivery for pregnancies achieved with IVF, we recommend shared decision-making between patients and healthcare providers when considering induction of labor at 39 weeks of gestation.	1C

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placental implantation disorders associated with IVF, because the major risk factors for vasa previa are velamentous cord insertion (OR, 672) and bilobed placenta (OR, 71),[72] both of which are increased in pregnancies achieved with IVF.

Placenta accreta spectrum is also more common following IVF, with numerous studies showing an adjusted risk of between 3 and 6 when compared with naturally occurring pregnancies.[73-78] IVF should be considered an additional risk factor for accreta in patients with placenta previa and a history of cesarean delivery. Patients with multiple risk factors should be evaluated for placenta accreta spectrum. The recently published Special Report of the Society for Maternal-Fetal Medicine Placenta Accreta Spectrum Ultrasound Marker Task Force provides definitions of diagnostic markers and recommended approaches to ultrasound examination in pregnancies at risk for placenta accreta spectrum.[79]

All of the above manifestations of placental implantation disorders appear to be related to each other and can occur together. Therefore**, we recommend that a careful examination of the placental location, placental shape, and cord insertion site be performed at the time of the detailed fetal anatomy ultrasound, including evaluation for vasa previa (GRADE 1B).** Targeted screening via transvaginal ultrasound should be considered in all pregnancies achieved with IVF with velamentous cord insertion, succenturiate or bilobed placentas, or resolved placenta previa to rule out vasa previa on the basis of the potentially catastrophic risks such a diagnosis implies and the >95% survival rates achieved with prenatal diagnosis.[80,81] Because of the ongoing risk of vasa previa in the setting of resolved placenta previa, reassessment for vasa previa is warranted when reassessing placental location at 32 weeks of gestation.

Is the prevalence of spontaneous preterm birth higher in pregnancies achieved with in vitro fertilization?

The risk for preterm birth is higher in all types of singleton gestations from ART.[82,83] A meta-analysis of singleton

Society for Maternal-Fetal Medicine Grading System: Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Recommendations[107,a]

Grade of recommendation	Clarity of risk and benefit	Quality of supporting evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Consistent evidence from well-performed, randomized controlled trials, or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on the confidence of the estimate of benefit and risk and may change the estimate.	Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C. Strong recommendation, low-quality evidence	Benefits seem to outweigh risks and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Weak recommendation; best action may differ depending on circumstances or patients or societal values.
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation, other alternatives may be equally reasonable.
Best practice	Recommendation in which either (1) there is an enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize) or (2) recommendation to the contrary would be unethical.		

[a] Adapted from Guyatt et al.[108]

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pregnancies demonstrated that IVF is associated with higher odds of preterm delivery (OR, 2.0; 95% CI, 1.7–2.2), low birthweight (OR, 1.8; 95% CI, 1.4–2.2), and very low birthweight (OR, 2.7; 95% CI, 2.3–3.1) when compared with naturally occurring pregnancies.[82] Indeed, preterm birth has been recognized for several decades as the primary independent cause of increased rates of several adverse neonatal outcomes, including neonatal encephalopathy and perinatal mortality, in pregnancies achieved with IVF. Such risks are more than doubled in the presence of IVF twin gestations. Among pregnancies achieved with IVF, the risk for preterm delivery may be associated with specific IVF techniques[83]; compared with natural-cycle IVF, live births after stimulated IVF cycles have significantly higher risks for preterm birth (RR, 1.27; 95% CI, 1.03–1.58) and low birthweight (RR, 1.95; 95% CI, 1.03–3.67).[84] Pregnancies achieved with IVF after oocyte donation have higher risks than those achieved with autologous oocytes.[85] Subfertility is also a major risk factor for prematurity.[83] However, even in the same patient, pregnancies achieved with ART have higher risks for preterm birth than naturally occurring pregnancies.[83] Although there may be an increased risk for spontaneous preterm birth with pregnancies achieved with IVF, the utility of serial cervical length measurement to screen for preterm birth risk is unknown when the sole indication is IVF. **Although visualization of the cervix at the 18 0/7 to 22 6/7 weeks of gestation anatomy assessment with either a transabdominal or endovaginal approach is recommended, we do not recommend serial cervical length assessment as a routine practice for pregnancies achieved with IVF (GRADE 1C).**[86,87] In addition, progesterone supplementation initiated for IVF cycles is not indicated after 12 weeks of gestation if it was solely initiated for IVF purposes without any other indication. Discontinuation of progesterone supplementation initiated for the sole purpose of IVF is recommended by 12 weeks.

Is the prevalence of fetal growth restriction higher in pregnancies achieved with in vitro fertilization?

An increased risk for small for gestational age (SGA) infants is documented for singleton pregnancies achieved with IVF,[7,83,88-90] with an OR of 1.4 (95% CI, 1.27–1.53) to 1.6 (95% CI, 1.3–2.0) in meta-analyses.[7,82] The difference in weight between IVF with or without ICSI and naturally occurring children persists from ages 0 to 4 years (mean difference, −180 g; 95% CI, −320 to −4), but the significance disappears in children after age 5 (mean difference, −160 g; 95% CI, −580 to 260).[91] The degree of the effect of IVF on fetal growth differs by IVF technique: meta-analyses have described a higher risk for SGA babies in pregnancies achieved via IVF with or without ICSI from fresh cycles than with frozen cycles.[83,92-94]

A retrospective cohort study reported the estimated fetal weight (EFW) for pregnancies achieved with IVF (with or without ICSI) decelerated in the third trimester when compared with reference growth curves, whereas that of frozen embryo transfer did not.[95] The effect on fetal growth is particularly evident near term.[89] The optimal gestational ages for fetal growth scans and their frequency in the presence of additional risk factors (eg, placental implantation anomalies or maternal age >40 years) is presently unknown. **We suggest that an assessment of fetal growth be performed in the third trimester for pregnancies achieved with IVF; however, serial growth ultrasounds are not recommended for the sole indication of IVF (GRADE 2B).**

In pregnancies achieved with in vitro fertilization, does low-dose aspirin prophylaxis reduce the risk for fetal and placental complications?

IVF and underlying infertility are associated with adverse perinatal outcomes, including hypertensive disorders of pregnancy.[96] A meta-analysis demonstrated an OR of 1.49 (95% CI, 1.39–1.59) for hypertensive disorders of pregnancy in pregnancies achieved using IVF with or without ICSI when compared with naturally occurring pregnancies.[7] However, the risk appears to depend on the specific IVF technique utilized. When compared with autologous IVF, oocyte donation is associated with a higher risk for hypertensive disorders of pregnancy (OR, 2.63; 95% CI, 2.17–3.18), preeclampsia (OR, 2.64; 95% CI, 2.29–3.04), preeclampsia with severe features (OR, 3.22; 95% CI, 2.30–4.49), and gestational hypertension (OR, 2.16; 95% CI, 1.79–2.62).[97] Meta-analyses show an increased risk for preeclampsia in pregnancies achieved with IVF from frozen embryo transfer when compared with fresh embryo transfer (risk ratio [RR], 1.79; 95% CI, 1.03–3.09).[98]

A meta-analysis did not find a significant reduction in the rates of hypertensive disorders of pregnancy or preterm delivery with prepregnancy initiation of low-dose aspirin (100 mg) in pregnancies achieved with IVF for singletons (OR, 0.62; 95% CI, 0.22–1.7) or twins (OR, 1.2; 95% CI, 0.35–4.4).[99] The United States Preventative Services Task Force states that IVF is a moderate risk factor for preeclampsia and recommends low-dose aspirin if an additional moderate risk factor is found.[100] **We do not recommend low-dose aspirin for patients with pregnancies achieved with IVF as the sole indication for preeclampsia prophylaxis; however, if one or more additional risk factors are present, low-dose aspirin is recommended (GRADE 1B).**

Is the prevalence of stillbirth increased in pregnancies achieved with in vitro fertilization?

Pregnancies achieved with IVF have a 2- to 3-fold increased risk for stillbirth even after controlling for maternal age, parity, and multifetal gestations.[82,101-103] One meta-analysis found a stillbirth rate of 11.8 per 1000 with an OR of 2.6 (95% CI, 1.8–3.6) in pregnancies achieved with IVF as compared with naturally occurring pregnancies.[82] The risk for stillbirth seems to be affected by whether the pregnancy

was achieved with frozen rather than fresh embryo transfer: a meta-analysis reported a lower risk for the former compared with the latter (RR, 0.88; 95% CI, 0.79–0.99).[93] The ACOG-SMFM Committee Opinion on Antenatal Fetal Surveillance suggests surveillance for conditions for which stillbirth is reported to occur more frequently than 0.8 per 1000 (the false-negative rate of a biophysical profile) and for which there is a relative risk or odds for stillbirth of >2.0 when compared with pregnant people without the condition.[104] **Given the increased risk of stillbirth, we suggest weekly antenatal fetal surveillance beginning by 36 0/7 weeks of gestation for pregnancies achieved with IVF (GRADE 2C).**[104]

In pregnancies achieved with in vitro fertilization, does delivery at 39 weeks of gestation reduce the risk for adverse perinatal outcomes?

It is currently unknown whether elective delivery at 39 weeks of gestation reduces the risks for maternal morbidity and improves perinatal outcomes in pregnancies achieved with IVF when compared with expectant management. A systematic review of published randomized controlled trials reveals that in asymptomatic uncomplicated singleton gestations, induction of labor between 39 0/7 and 40 6/7 weeks of gestation does not increase the risk for cesarean delivery when compared with expectant management (18.6% vs 21.4%; RR, 0.96; 95% CI, 0.78–1.19), but it does not reduce the rates of adverse perinatal outcomes, including perinatal death (OR, 0.51; 95% CI, 0.13–2.08), low Apgar score at 5 minutes, or the need for neonatal intensive care unit admission.[105] **In the absence of studies focused specifically on timing of delivery for pregnancies achieved with IVF, we recommend shared decision-making between patients and healthcare providers when considering induction of labor at 39 weeks of gestation (GRADE 1C).**[106]

Conclusion

IVF is associated with an increased risk for several adverse maternal and perinatal outcomes. However, evidence is limited regarding whether specific screening, diagnostic, or preventative interventions during pregnancy obviate or reduce such risks. Specific technical characteristics of IVF (eg, whether the eggs were autologous or donated; whether the IVF cycle was natural vs stimulated; the type of PGT that was performed; whether the embryos transferred were fresh or frozen; and whether ICSI or conventional IVF was performed), in addition to the presence of underlying infertility, affect the risks for adverse clinical outcomes. Therefore, individualization of care may be ideal for optimizing outcomes.

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