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

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

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Condensation: This Consult discusses the management of pregnancies achieved by in vitro fertilization and provides recommendations based on the available evidence.

Abstract: 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 of 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 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 counseling be offered regarding the option of multifetal pregnancy reduction (GRADE 1C); (5) we recommend 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 fetal echocardiography be offered to patients with pregnancies achieved with in vitro fertilization and intracytoplasmic sperm injection (GRADE 2C); (7) we recommend 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 an assessment of fetal growth 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 one or more additional risk factors are present, low-dose aspirin is recommended (GRADE 1B); (11) given the increased risk of 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) resulting in 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 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

of 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) as well as maternal conditions associated with subfertility and infertility (including advancing maternal age and reduced ovarian reserve). It is often impossible to separate the individual factors affecting risks of 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 for patients considering or who have undergone IVF?

The IVF procedure itself does not appear to lead to a higher prevalence of chromosomal anomalies when compared with naturally occurring pregnancy.[9,10] However, several other factors may play a role in the increased risk of chromosomal anomalies in these pregnancies, including advanced maternal age and polycystic ovary syndrome.[11,12] Severe male and female factor infertility may be associated with a higher risk of 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 since 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.[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 compared with the IVF alone-treated group (1.3% versus 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.[18] Similar findings have been reported by other groups.[19]

Patients with reduced ovarian reserve and primary ovarian insufficiency have an increased risk of 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/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 compared with naturally occurring pregnancy 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 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 prior to transfer has been proposed to increase implantation and pregnancy rates per transfer and lower miscarriage rates. Most recent techniques involve molecular testing of all chromosomes using quantitative polymerase chain reaction (qPCR), microarray technology, or next-generation sequencing on several trophoectoderm cells sampled from day 5-6 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 one systematic review of 26 studies that compared 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 a result of including 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, as well as the known biological and human factors that may lead to misdiagnosis. Misdiagnoses can be due to unprotected sex during the IVF cycle, human error (transfer of a wrong embryo), or postzygotic mitotic changes. False-negative diagnoses may be due to contaminating extraneous DNA, allele drop-out, or partial amplification and may result in the transfer of abnormal embryos. Despite these limitations, reported misdiagnosis rates are less than 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).**

Further, embryo mosaicism is present in an estimated 16% to 21% of blastocysts.[41] If euploid embryos are unavailable, aneuploid mosaic embryos are sometimes transferred, as 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, 15), the risk of clinically significant uniparental disomy via trisomy/monosomy rescue mechanisms averages about 5%.[43] Prenatal diagnostic testing should be offered to patients with pregnancies that occur from 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 IVF?

The accuracy of first-trimester genetic screening tests for aneuploidies may be affected by IVF. In a recent systematic review, 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 AFP and transcription factor μE3 and increased total hCG in the second trimester.[45] Another meta-analysis confirmed the lower PAPP-A levels in IVF/ICSI versus controls, IVF versus controls, and ICSI versus controls but did not find a significant difference in NT measurements.[46] These findings suggest a potential increased risk of false-positive results for aneuploidies in patients who undergo first trimester combined screening.[47]

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

Are congenital anomalies increased in pregnancies achieved with IVF?

Meta-analyses demonstrate associations between IVF/ICSI and congenital malformations, although it remains unclear if this association is due to infertility, factors associated with the procedure, or both.[54-56] It is also difficult to distinguish the risk associated with IVF alone versus 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/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. Table 1 displays pooled estimates for specific malformations as derived from a meta-analysis.[54]

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

Additionally, a systematic review reported higher rates of total congenital heart disease (CHD) in the IVF/ICSI population compared with 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 due at least in part to 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, universal fetal echocardiography in pregnancies achieved by IVF was associated with a higher detection rate for CHDs compared with screening only when abnormal cardiac findings were noted on a detailed anatomy scan. Therefore, **we suggest fetal echocardiography be offered to patients with pregnancies achieved with IVF and ICSI (GRADE 2C).**[65]

Are placental anomalies increased in pregnancies achieved with IVF?

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 from

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

Placenta accreta spectrum is also more common following IVF, with numerous studies showing an adjusted risk between 3 and 6 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 related to each other and can occur together. Therefore**, we recommend 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 sonogram 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, given the potentially catastrophic risks such a diagnosis implies, as well as the >95% survival rates achieved with prenatal diagnosis.[80,81] Due to 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 IVF?

The risk of preterm birth is higher in all types of singleton gestations from ART.[82,83] A meta-analysis of singleton 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) 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 of preterm delivery may be associated with specific IVF techniques;[83] live births after stimulated IVF cycles have significantly higher risks of preterm birth and low birthweight compared with natural-cycle IVF.[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 of 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 IVF?

An increased risk of 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/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, 260).[91] The degree of the effect of IVF on fetal growth differs by IVF technique: meta-analyses have described a higher risk of SGA babies in pregnancies achieved wth IVF/ICSI from fresh cycles compared with frozen cycles.[83,92-94]

A retrospective cohort study reported that in the third trimester, estimated fetal weight (EFW) was significantly lower for pregnancies achieved with IVF (with or without ICSI), whereas only frozen-embryo transfer singletons had a greater EFW compared with reference growth curves.[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 an assessment of fetal growth 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 IVF, does low-dose aspirin prophylaxis reduce the risk of 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 IVF/ICSI 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 of hypertensive disorders in 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 of preeclampsia in pregnancies achieved with IVF from frozen embryo transfer 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 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 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 IVF?

Pregnancies achieved with IVF have a two to three-fold increased risk of 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 1,000 with an OR of 2.6 (95% CI,1.8-3.6) in pregnancies achieved with IVF compared with naturally occurring pregnancies.[82] The risk of stillbirth appears 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 1,000 (the false-negative rate of a biophysical profile) and for which there is a relative risk or odds for stillbirth of more than 2.0 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 IVF, does delivery at 39 weeks reduce the risk of adverse perinatal outcomes?

It is currently unknown whether elective delivery at 39 weeks reduces the risks of maternal morbidity and improves perinatal outcomes in pregnancies achieved with IVF 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 does not increase the risk of cesarean delivery compared with expectant management (18.6% vs 21.4%; RR 0.96; 95% CI, 0.78-1.19) but 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 need for NICU 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]**

Conclusions

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 of adverse clinical outcomes. Therefore, individualization of care may be ideal for optimizing outcomes <Unnumbered tables 1 and 2 here>.

390 **<Unnumbered table 1>Summary of Recommendations**

Number	Recommendations	GRADE
1	We suggest 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 counseling be offered regarding the option of multifetal pregnancy reduction.	1C
5	We recommend a detailed obstetrical ultrasound examination (CPT 76811) be performed for pregnancies achieved with IVF and ICSI .	1B
6	We suggest fetal echocardiography be offered to patients with pregnancies achieved with IVF and ICSI.	2C

7	We recommend 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 IVF pregnancies.	1C
9	We suggest an assessment of fetal growth in the third trimester for IVF pregnancies; 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 of 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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392 **<Unnumbered table 2>Society for Maternal-Fetal Medicine Grading System: Grading of**

393 **Recommendations Assessment, Development, and Evaluation (GRADE) Recommendations**

394 **107, a**

395

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	Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale

		likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.	for an alternative approach is present.
1C. Strong recommendation, low-quality evidence	Benefits appear 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 (i) 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 (ii) recommendation to the contrary would be unethical.		

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

Table 1. Pooled estimates of rates (per 1,000) for specific congenital anomalies in singleton pregnancies following IVF +/- ICSI compared with naturally occurring pregnancies (95% CI)

Organ system	**IVF/ICSI pregnancies**	**Naturally occurring pregnancies**
Cleft lip/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 L, Yang T, Zheng Z, Yu H, Wang H, Qin J. Birth prevalence of congenital malformations in singleton pregnancies resulting from in vitro fertilization/intracytoplasmic sperm injection worldwide: a systematic review and meta-analysis. Arch Gynecol Obstet 2018;297:1115-30.

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SMFM Consult #60 - Management of pregnancies resulting from in-vitro fertilization (IVF) – Summary of Evidence Table

Clinical question		
What genetic conditions should be discussed for patients considering or who have undergone IVF?		
Recommendation statement		
We suggest genetic counseling be offered to all patients undergoing or who have undergone IVF with or without ICSI.		
GRADE		
2C - 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.		
Other organization recommendations		
n/a		
Category A Evidence:	Category B Evidence:	Category C Evidence:
n/a	**Lazaraviciute 2014**: Systematic review and meta-analysis of 18 observational studies. The combined odds ratio (95% confidence intervals) of any imprinting disorder in children conceived through ART was 3.67 (1.39, 9.74) in comparison with spontaneously conceived children. **Cortessis 2018**: Systematic review and meta-analysis of 13 reports from 23 studies. For pregnancies after ART compared with naturally occurring pregnancies: Angelman syndrome, summary odds ratio (sOR) = 4.7 (95% CI 2.6–8.5, 4 studies); Beckwith-Wiedemann syndrome, sOR = 5.8 (95% CI 3.1–11.1, 8 studies); Prader-Willi syndrome, sOR = 2.2 (95% CI 1.6–3.0, 6 studies); Silver-	**Aboulghar 2001**: Prospective cohort study. Karyotypes of 430 babies conceived through ICSI compared with 430 babies conceived naturally. 15/430 (3.5%) ICSI babies vs 0/430 (0%) normally conceived babies had abnormal karyotypes (p<0001). Of 15 abnormal karyotypes, 6 were sex chromosome anomalies, 8 had autosomal anomalies, 1 had combined sex chromosome and autosomal anomalies. **Belva 2020:** Cohort study. 4816 ongoing ICSI pregnancies; 4267 of which had pregnancy outcome data. Prenatal testing was performed in 22.3% of the pregnancies, resulting in a diagnosis in 1114 fetuses. An abnormal fetal karyotype was found in 29

	Russel syndrome, sOR = 11.3 (95% CI 4.5–28.5, 3 studies).	singletons and 12 multiples (41/1114; 3.7%; 95% CI 2.7–4.9%): 36 anomalies were de novo (3.2%; 95% CI 2.3–4.4), either numerical (n=25), sex (n=6) or structural (n=5), and five were inherited. In all but one case, fetuses with an abnormal karyotype were conceived by ICSI using ejaculated sperm. **Bonduelle 2002**: Observational study. Fetal karyotypes of 2622 ICSI with fresh embryo transfer pregnancies, comparing origin and characteristics of sperm used for ICSI. 698 fetuses were tested with CVS; 888 were tested by amniocentesis. Abnormal fetal karyotypes were found in 47 samples [3.0%; 95% CI 2.2–3.9%]; 25 anomalies (1.6%; 95% CI 1.0–2.3%) were de novo. 10 were sex chromosome anomalies; 15 were autosomal anomalies; 22 were inherited abnormalities. A significantly higher percentage of 2.1% de-novo prenatal chromosomal anomalies was observed for sperm concentrations of <20 x 10^6 sperm per ml, as compared with 0.24% if the sperm concentration was ≥20 x 10^6 sperm per ml (Fisher's exact test, P = 0.006). **DeBaun 2003**: Prospective cohort study of US BWS registry data. Prevalence of ART among BWS cohort was 4.6% (3 of 65), versus the background rate of 0.8% in the United States. 7 children with BWS were born after ART—five of whom were conceived after ICSI. Molecular studies of six of the children indicate that five of the six have specific

		epigenetic alterations associated with BWS—four at LIT1 and one at both LIT1 and H19. **Gjerris 2008:** Cohort study of Danish national pregnancy registry data. 8531 ART pregnancies (6122 IVF, 2087 ICSI and 322 'IVFICSI'). Rate of prenatal invasive procedures: 16.3%; uptake of second trimester serum screening: 7.4%. The rate of karyotype aberrations detected by prenatal testing was 2.7% (43/1586); the overall rate of pre- and post-natally detected aberrations was 0.6% (62/9625). Chromosome aberrations were more common in the ICSI-treated group compared with the IVF-treated group [1.3% (30/2297) versus 0.5% (32/6957), P < 0.0001]. **Hattori 2019**: Cohort study. 931 patients with imprinting disorders (117 BWS, 227 AS, 520 PWS, and 67 SRS). Found 4.46-, 8.91-, 3.44-fold increased frequencies of BWS, SRS, and PWS associated with ART compared with spontaneous conception. **Tiboni 2011**: Observational study. Karyotype analysis of 1,146 couples referred to ART. The overall frequency of chromosome aberrations was 1.52%. The prevalence of aberrations was comparable among the two genders: 14 cases (1.22%) in women; 21 cases (1.83%) in men. Of the couples in whom an abnormality was detected, 3 declined ART treatment, 32 underwent ICSI,

		and 12 (34.28%) achieved clinical pregnancy. Five pregnancies ended in spontaneous abortion during the first trimester; 7 pregnancies ended in delivery of 4 singleton and 6 twin infants. **Uk 2018**: Retrospective cohort study. 46 cases of epigenetic diseases were analyzed from French congenital malformation registry. 4/46 cases were from pregnancies induced by ART. ART was a risk factor for epigenetic disease (OR=2.9 [1.06–8.22] (p=.039)). In ART-pregnancies there were 2 diagnoses: Beckwith-Wiedemann syndrome (3/4) and Silver-Russell syndrome (1/4). **Chandley 1998**: Literature review. Among the 10% or so of men who are diagnosed as oligo- or azoospermic in the absence of any physical obstruction, research is now showing that between 8 and 15% carry a microdeletion in the long arm of the Y chromosome which, by loss of specific DNA segments, leads to loss of vital genes for sperm production. Chromosomal anomalies account for ~2% of all men who attend infertility clinics, rising to 15% among those with azoospermia. **Gosden 2003:** Literature review. 3 recent studies report an unexpectedly high incidence of BWS in children conceived with ARTs. Six of 149 cases were reported from a British BWS registry; the same numbers were recorded in a French registry; and a further

		seven children have been reported in the USA. **Katagiri 2021:** Literature review. The frequency of chromosome abnormalities in infertile patients is 0.595%-0.64%. For couples who are treated with ART, the incidences of chromosomal abnormalities are 1.2%-2.1% in female and 1.1%-6.1% in male; and 3.8-18.4% in severe oligospermia and 14.7-35% in azoospermia. **Vermeiden 2013**: Literature review; 8 epidemiological studies. Following IVF or ICSI compared with normal population, weighted relative risk of BWS = 5.2 (95% CI 1.6-7.4). No significant associations were found between the incidences of the Angelman and Prader-Willi syndromes and IVF or ICSI treatments. Data were insufficient on SRS to draw a conclusion.

Clinical question
What are the different types of preimplantation genetic testing?
Recommendation statement
Regardless of whether PGT has been performed, we recommend all patients who have achieved pregnancy with in vitro fertilization be offered prenatal genetic screening and diagnostic testing via chorionic villus sampling or amniocentesis.
GRADE

1C- Benefits appear 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.

Other organization recommendations

ASRM 2018: Non-systematic guideline. The value of PGT-A as a universal screening test for all IVF patients has yet to be determined… Large, prospective, well-controlled studies evaluating the combination of multiple approaches (genomics, time-lapse imaging, transcriptomics, proteomics, metabolomics, etc.) for enhanced embryo selection applicable in a more inclusive IVF population are needed to determine not only the effectiveness, but also the safety and potential risks of these technologies.

ACOG CO 799: Confirmation of preimplantation genetic testing-monogenic results with chorionic villus sampling (CVS) or amniocentesis should be offered.

Gleicher 2020: Consensus opinion of the International Do No Harm Group in IVF. we recommend restrictions to the increasing, and by IVF centers now often even mandated, utilization of PGT-A in IVF cycles. While PGT-A has been proposed as a tool for achieving enhanced singleton livebirth outcomes through embryo selection, continued false-positive rates and increasing evidence for embryonic self-correction downstream from the testing stage, has led IDNHG-IVF to conclude that currently available data are insufficient to impose overreaching recommendations for PGT-A utilization.

Category A Evidence:	Category B Evidence:	Category C Evidence:
Marin 2021: Systematic review of 26 studies describing concordance of initial PGT-A and reanalysis results in 1271 human blastocysts from 2260 pairwise comparisons. Concordance rates were 93.8% for euploidy, 81.4% for full aneuploidy, and 42.6% for mosaic aneuploidy (all $p<0.05$).	n/a	**Harris 2020**: Literature review evaluating PGT-A, PGT-M, PGT-SR. Concluded that significant advances have been made in the ability to analyze human embryos for genetic abnormalities, but optimization of these molecular techniques remains necessary to decrease the false positive rates. **Popovic 2020**: Observational study. 1 ICM and 3 TE samples each were taken from unknown embryos (n=34) and abnormal or mosaic PGT-A blastocysts (n=24) to assess chromosomal profile. Concordance between the ICM and all TE portions was established in

		62.1% of blastocysts, across both embryo groups. **Sciorio 2020**: Editorial. Concluded that the diagnosis of embryo aneuploidies in IVF cycles should be considered as a research tool and systematic implementation in clinical practice may appear unjustified. **Carson 2021**: Literature review. Concluded that although several RCTs support this practice, considerable controversy exists regarding the efficacy of preimplantation genetic testing as a universal screening test for all patients undergoing IVF. **Hardy 2020**: Literature review. Concluded that the recommendation for confirmatory prenatal diagnostic testing has remained a standard component of PGT-M counseling, reflecting the inherent difficulties of testing the limited number of cells obtained from embryo biopsy, as well as recognition of the biological and human factors that may lead to misdiagnosis in a PGT-M cycle.

Clinical question
What is the accuracy of 1st trimester genetic screening tests in IVF pregnancies?
Recommendation statement

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- 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.		
Other organization recommendations		
n/a		
Category A Evidence:	Category B Evidence:	Category C Evidence:
Lanes 2016: Systematic review. 29 cohort and 11 case-control studies comparing IVF and natural pregnancies. A decrease in PAPP-A and an increase in total hCG was consistently reported among the included studies. Results for free beta-HCG, AFP, uE3, and DIA varied. **Cavoretto 2017**: Systematic review. 27 articles included in qualitative synthesis; 11 articles included in quantitative synthesis. Free beta-HCG test showed slightly higher values in the ICSI group than controls (RR = 1.09, 95%CI: 1.03–1.16) but not in the IVF group (RR = 1.03, 95%CI: 0.94–1.12). PAPP-A values for IVF/ICSI, IVF and ICSI showed lower values in comparison with controls (RR, 95%CI 0.85, 0.80–0.90; 0.82, 0.74–0.89 and 0.83, 0.79–0.86, respectively). The NT measurement did not show any statistical differences between study groups (IVF and ICSI) and controls (RR = 1.00, 95%CI: 0.94–	n/a	**Lee 2018**: Retrospective cohort study. 4633 spontaneous and 992 IVF pregnancies undergoing cfDNA testing. Median fetal fraction was lower (10.3% [IQR, 7.7–13.5] versus 11.9% [IQR, 9.1–15.0]; P = 0.005), test failure rate was higher (5.2 versus 2.2%; P < 0.001) and PPV for trisomies 18, 13 and sex chromosome anomalies was poorer in IVF pregnancies compared to those spontaneously conceived. Multivariate linear regression analysis demonstrated that IVF conception, increased BMI, earlier gestational age and South and East Asian ethnicities were independent predictors of lower fetal fraction. Multiple logistic regression analysis found IVF conception and increased BMI to be independently associated with test failure. **Rizzo 2016**: Observational study. 266 IVF pregnancies (fresh and frozen embryos) compared with 266 spontaneous

1.08 and RR = 1.01, 95%CI: 0.97–1.05, respectively). **Gjerris 2012**: Systematic review. 61 articles. For IVF/ICSI singletons, combined first trimester prenatal screening based on maternal age, nuchal translucency scan and biomarkers is appropriate. However, biomarkers seem to be altered, causing a higher false-positive rate, in IVF/ICSI singleton gestations.		pregnancies; evaluating uterine artery PI and 3D placental volume measured at 11 0/7 to 13 6/7 weeks of gestation. No differences were found in uterine artery PI MoM between the 3 groups. Placental volume was significantly lower in both IVF groups when compared to the controls (fresh embryo IVF, Z = 9.33; P ≤ .0001; frozen-thawed embryos IVF, Z = 3.1; P= .04). The IVF pregnancies with fresh embryos showed placental volume MoM values significantly lower than in the frozen-thawed embryo IVF pregnancies (U = 5.4; P ≤ .0001) **White 2019**: Observational study. 2904 patients with 2906 unique pregnancies undergoing cfDNA testing; evaluating a sample submitted for repeat testing after an initial test with an insufficient fetal fraction. 53% of pregnancies obtained a result on the second draw. The odds of obtaining a result were associated with interval time between draws (per day, OR 1.040, 95% CI 1.031–1.051) and maternal weight (per kg, OR 0.988, 95% CI 0.985–0.991) but not maternal age, gestational age at initial draw, IVF status, or twin versus singleton pregnancy.

Clinical question
Does multifetal pregnancy reduction (MFPR) reduce the risks associated with multiple gestations?

Recommendation statement		
When multifetal pregnancies do occur, we recommend counseling be offered regarding the option of multifetal pregnancy reduction.		
GRADE		
1C - Benefits appear 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.		
Other organization recommendations		
ACOG CO 719: Non-systematic guideline. Nondirective patient counseling should be offered to all women with higher-order multifetal pregnancies and should include a discussion of the risks unique to multifetal pregnancy as well as the option to continue or reduce the pregnancy. Resources for providing such counseling can include maternal–fetal medicine specialists, neonatologists, mental health professionals, child development specialists, support groups, and clinicians with procedural expertise in multifetal pregnancy reduction.		
Category A Evidence:	Category B Evidence:	Category C Evidence:
n/a	**Qin 2017:** Systematic review and meta-analysis of 64 studies with 60,210 IVF/ICSI multiple births and 146,737 spontaneously conceived multiple births. There was a similar prevalence of poor outcomes among multiple births conceived with IVF/ICSI and naturally (all P ≥ 0.0792). **Hviid 2018:** Systematic review and meta-analysis of 38 original studies, 11 of which included in the MA of 161,885 pregnancies. Factors associated with monozygotic twinning: blastocyst transfer compared with cleavage-stage embryos transfer: odds ratio = 2.18, 95% CI: 1.93–2.48; younger compared with older maternal age.	n/a

Clinical question
Are congenital anomalies increased in IVF pregnancies?
Recommendation statement
We recommend a detailed obstetrical ultrasound examination (CPT 76811) be performed pregnancies achieved with in vitro fertilization and intracytoplasmic sperm injection.
GRADE
1B - 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 confidence in the estimate of benefit and risk and may change the estimate.
Other organization recommendations
AIUM 2019: Indications for a detailed fetal anatomic examination include, but are not limited to, the following conditions: Fetus at increased risk for a congenital anomaly, such as the following: Pregnancy conceived via assisted reproductive technology.

Category A Evidence:	Category B Evidence:	Category C Evidence:
n/a	**Chen 2018:** Systematic review and meta-analysis, including 34 cohort studies of 159,021 IVF/ICSI and 6704,405 spontaneously conceived singleton pregnancies. Among IVF/ICSI singleton pregnancies, pooled estimates of total congenital malformations (CMs) and major CMs (per 10,000) were 484.3 (95% CI 363.8–641.9) and 475.8 (95% CI 304.9–735.2). Among spontaneous singleton pregnancies, pooled estimates of total CMs and major CMs (per 10,000) were 326.4 (95% CI 231.4-458.6) and 317.6 (95% CI 145.2-680.8).	**Davies 2012**: Retrospective cohort of 308,974 births, 6163 from assisted conception. The unadjusted odds ratio for any birth defect in pregnancies involving assisted conception (513 defects, 8.3%) as compared with pregnancies not involving assisted conception (17,546 defects, 5.8%) was 1.47 (95% confidence interval [CI], 1.33 to 1.62); the multivariate-adjusted odds ratio was 1.28 (95% CI, 1.16 to 1.41). **Henningsen 2018:** Retrospective cohort of 90,201 singleton ART children and 482,552 singleton children conceived spontaneously.

	Hoorsan 2017: Systematic review and meta-analysis, including 30 studies of 315,402 infants conceived by ART and 5,154,779 infants spontaneously conceived. For ART vs spontaneous conception, OR was higher for cardiac abnormalities 1.43 (95% CI, 1.27 to 1.62), CNS abnormalities 1.36 (95% CI, 1.10 to 1.70), GU abnormalities 1.58 (95% CI, 1.28 to 1.94), musculoskeletal disorders 1.35 (95% CI, 1.12 to 1.64), and chromosomal abnormalities 1.14 (95% CI, 0.90 to 1.44). **Wen 2012**: Meta-analysis, including 46 studies of children conceived by IVF/ICSI (n=124,468) and spontaneously. Pooled risk estimate for birth defects = 1.37 (95% CI 1.26–1.48).	Absolute risk for major malformation was 3.4% among ART vs. 2.9% among spontaneously conceived.
Recommendation statement		
We suggest fetal echocardiography be offered to patients with pregnancies achieved with in vitro fertilization and intracytoplasmic sperm injection.		
GRADE		
2C - 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.		
Other organization recommendations		
AIUM 2020: Non-systematic consensus guideline. Fetal echocardiography is indicated if there is: In vitro fertilization, including ICSI.		
Category A Evidence:	Category B Evidence:	Category C Evidence:
n/a	**Giorgione 2018**: Systematic review and meta-analysis, including 25 856 children conceived	**Tararbit 2013**: Case-control study, including 1583 cases of CHD and 4104 malformed

	from IVF/ICSI techniques and 287 995 children conceived spontaneously. Total CHD events were 337/25 856 (1.30%) and 952/287 995 (0.68%) in the IVF/ICSI and spontaneous conception groups, respectively. The risk of CHD was significantly increased in the IVF/ICSI group as compared with the spontaneous conception group (pooled OR, 1.45; 95%CI, 1.20–1.76; P=0.0001; I2 =44%; P=0.08).	controls with no known associations with ART. Exposure to ART was significantly higher for tetralogy of Fallot than controls (6·6 vs. 3·5%, P=0·002); this was not the case for HLHS, transposition of great arteries, or coarction of the aorta. **Liberman 2017**: Retrospective cohort study, including 17,829 ART-exposed births, 355 of which had a birth defect, compared with 162 of 9431 births to subfertile mothers and 6183 of 445,080 births to fertile mothers. Elevated rates of tetralogy of Fallot and hypospadias were observed with ART, with multiple births explaining 36% of the relative effect of ART on nonchromosomal birth defects. **Bjorkman 2021**: Retrospective cohort study, including 181,749 live births. Fetal echocardiography was performed in 2,230 IVF pregnancies. The odds ratio for CHD in the IVF group compared with statewide population rates was 1.4 (95% CI 0.9–2.1). Four defects were clinically significant, indicating that 510 fetal echocardiograms were performed for every diagnosis of one clinically significant CHD in the IVF group. **Chung 2021**: Cost-effectiveness study of 3 screening strategies for CHD: (1) anatomic ultrasound (US): selective fetal echo following abnormal cardiac findings on detailed anatomic survey; (2) ICSI only: fetal echo for all pregnancies following IVF with

		ICSI; (3) all IVF: fetal echo for all IVF pregnancies. The average base-case cost of each strategy was: anatomic US, $8119; ICSI only, $8408; and all IVF, $8560. The effectiveness of each strategy was: anatomic US, 1.74487 QALYs; ICSI only, 1.74497 QALYs; and all IVF, 1.74499 QALYs. It was determined that it would cost society five times more to detect one additional major CHD through intensive screening of all IVF pregnancies than it would cost to pay for the neonate's first year of care.

Clinical question
Are placental anomalies increased in IVF pregnancies?
Recommendation statement
We recommend 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 - 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 confidence in the estimate of benefit and risk and may change the estimate.
Other organization recommendations
SMFM 2015: Non-systematic guideline. Ultrasound evaluation of placental location and the relationship between the placenta and internal cervical os should be included at the second-trimester ultrasound scan, and the placental cord insertion site should be documented when technically possible.

Category A Evidence:	Category B Evidence:	Category C Evidence:
n/a	**Karami 2018:** Meta-analysis, including 24 studies of 1,377,893 pregnancies. Increased risk of placenta previa was observed for ART vs spontaneous singleton pregnancies: OR = 2.67 (95%CI: 2.01, 3.34) and RR = 3.62 (95%CI: 0.21, 7.03). **Ruiter 2016**: Systematic review, including 569 410 patients with 325 cases of vasa previa (VP). 2 studies reported on ART and VP. Women who conceived by ART had an increased risk of VP compared with women who conceived spontaneously (common OR 19; 95% CI 6.6–54, heterogeneity = 29%) **Roque 2018**: Systematic review and meta-analysis of 6 studies of IVF pregnancies. There was an increased risk of placenta accreta (aOR 3.51, 95% CI 2.04-6.05) for frozen compared with fresh embryo transfer groups, but there were no significant differences in the risk of placenta previa (aOR 0.70; 95% CI 0.46-1.08).	**Jauniaux 2020**: Literature review. IVF increases the risk for PAS between 4- to 13-fold compared with spontaneous pregnancy. IVF singleton pregnancies have a higher incidence of marginal cord insertion, VCI, and VP compared with spontaneously conceived singletons. ARTs, and in particular IVF, have also been associated with a higher incidence of placenta previa independently of the high rate of multiple pregnancies. **Sacha 2020**: Retrospective cohort of placental pathology from 1140 IVF live births. Frozen transfers (vs fresh transfers) were more likely to be associated with marginal cord insertion (aOR, 1.87; CI, 1.21, 2.91; P = .01), accessory lobe formation (aOR, 2.96; CI, 1.12, 7.79; P = 0.03), subchorionic thrombi (aOR, 3.72; CI, 1.80, 7.71; P < .001), and fetal vascular malperfusion characteristics with cord anomalies (aOR, 2.34; CI, 1.22, 4.46; P = .01). **Ginstrom Ernstad 2016**: Retrospective cohort study of 4819 singletons born after blastocyst transfer, 25,747 after cleavage-stage transfer, and 1,196,394 after spontaneous conception. The risk of placenta previa and placental abruption was higher in pregnancies after blastocyst transfer as compared to pregnancies after cleavage-stage (AOR, 2.08; 95% CI, 1.70-2.55 and AOR, 1.62; 95% CI,

		1.15-2.29, respectively) and spontaneous conception (AOR, 6.38; 95% CI, 5.31-7.66 and AOR, 2.31; 95% CI, 1.70-3.13, respectively). **Baulies 2007**: Retrospective cohort study of 12,063 deliveries: 824 of which were the result of IVF; 9 of which had vasa previa. 4/9 pregnancies with vasa previa were the result of IVF. **Sullivan 2017**: Prospective cohort study. 63 women identified with vasa previa, yielding estimated incidence of 2.1 per 10,000 women giving birth (95% CI 1.7–2.7/10,000). Use of ART was reported for 11 women, all of whom had at least one placental abnormality. **Modest 2020**: Retrospective cohort study of 28,344 pregnancies, 1,418 of which were ART. The overall incidence of PAS was 0.4% (2.2% in the IVF group and 0.3% in the non-IVF group). Women who underwent IVF had 5.5 times the risk of PAS (95% confidence interval [CI]: 3.4–8.7) compared with women in the non-IVF group, adjusted for maternal age, nulliparity, and year of delivery. **Kaser 2015**: Case-control study of 1571 IVF/ICSI patients evaluated for PAS. In multivariate analysis, we observed a significant association between cryopreserved embryo transfer and accreta (adjusted OR 3.20, 95% CI 1.14–9.02), which remained when analyses were restricted to

		cases of accreta with morbid complications (adjusted OR 3.87, 95% CI 1.08–13.81). **Salmanian 2020**: Retrospective cohort study of 37,461 deliveries: 281 had placenta previa in a first pregnancy; 571 had IVF; 5464 had history of CD. Frequency of PAS was 0.6%. Independent risk factors for placenta accreta spectrum were IVF (AOR, 8.7; 95% CI, 3.8-20.3), history of previous CD (AOR, 21.1; 95% CI, 11.4-39.2), and presence of placenta previa (AOR, 94.6; 95% CI, 29.3-305.1). After adjustment for number of previous CD, the correlation persisted for IVF (AOR 6.7, 95% CI 2.9-15.6). **Sundheimer 2018**: Retrospective cohort study of 3613 pregnancies. PAS was significantly higher in the patients receiving fertility treatments (1.2 versus 3.6%, $p < 0.05$) compared with spontaneous pregnancies. **Thurn 2016**: Prospective cohort study of 605,362 pregnancies, including 205 cases of abnormally invasive placenta (AIP). IVF was not recognized as a risk factor for AIP.

Clinical question
Is the prevalence of spontaneous preterm birth higher in IVF pregnancies?
Recommendation statement

Although visualization of the cervix at the 18 0/7-22 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 - Benefits appear 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.
Other organization recommendations
ACOG PB 130: Non-systematic guideline. Although this document does not mandate universal cervical length screening in women without a prior preterm birth, this screening strategy may be considered.

Category A Evidence:	Category B Evidence:	Category C Evidence:
n/a	n/a	n/a

Clinical question
Is the prevalence of fetal growth restriction higher in IVF pregnancies?
Recommendation statement
We suggest an assessment of fetal growth in the third trimester in pregnancies achieved with in vitro fertilization, however, serial growth ultrasounds are not recommended for the sole indication of IVF.
GRADE
2B - 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 confidence in the estimate of benefit and risk and may change the estimate.
Other organization recommendations

n/a		
Category A Evidence:	Category B Evidence:	Category C Evidence:
n/a	**Pandey 2012**: Systematic review and meta-analysis, including 30 cohort studies of IVF/ICSI vs spontaneous pregnancies. IVF/ICSI was associated with risk for LBW (RR=1.65, 1.56–1.75) and SGA (RR=1.38, 1.27-1.53) compared with spontaneous pregnancy. **Jackson 2005**: Meta-analysis, including 15 studies of 12,283 IVF and 1.9 million spontaneously conceived singletons. Compared with spontaneous, IVF was associated with significantly higher odds of LBW (OR 1.8; 95% CI 1.4, 2.2), very LBW (OR 2.7; 95% CI 2.3, 3.1) and SGA (OR 1.6; 95% CI 1.3, 2.0). **Pinborg 2012**: Systematic review and meta-analysis, including 65 studies of ART compared with spontaneous pregnancies. Found that frozen embryo transfer singletons have significantly lower adjusted risks of LBW and SGA and significantly higher adjusted risk of LGA than singletons born after IVF/ICSI with fresh embryo transfer. **McDonald 2009**: Systematic review and meta-analyses, including 17 studies of 31,032 singletons conceived through IVF (with or without ICSI) and 81,119 spontaneously conceived singletons. IVF was associated with increased risk of LBW (<2500 g, RR 1.60, 95% CI 1.29, 1.98).	**Ginod 2018:** Retrospective cohort study of 96 IVF, 210 ICSI, 121 frozen embryo transfer (FET), and 133 IUI pregnancies. At 11-13 wks, the crown rump length was longer than the reference curve whatever the assisted reproductive technique. At 21-23 6/7 wks, EFW was significantly greater for all groups compared with the reference curve, and at 31-33 6/7 wks, only FET singletons had a greater EFW. **De Geyter 2006:** Prospective cohort study of 443 spontaneous singleton pregnancies and 298 ART pregnancies. Lower birthweight observed for ART vs spontaneous conceptions at 37-39 wks (3199.3g vs 3322.3g) and 40-41 wks (3389.2g vs 3483.8g). **D'Angelo 2011**: Retrospective cohort study of 16,748 women attempting conception, 10.9% of whom used infertility treatment. ART pregnancies had increased odds of LBW (crude odds ratio [cOR]: 2.10, CI: 1.58, 2.79) and SGA (cOR: 1.72, CI: 1.13, 2.61) compared with no treatment. **Wennerholm 2013**: Retrospective cohort study of singletons born after frozen embryo transfer (n=6647) compared with singletons born after fresh IVF and ICSI (n = 42 242) and singletons born after spontaneous conception (n = 288 542). Singletons born

	Bay 2019: Systematic review and meta-analysis, including 13 studies of 3972 children born after IVF/ICSI and 11,012 spontaneously conceived children. IVF/ICSI children aged 0–4 years had significantly lower weight than spontaneously conceived children (Mean Diff -180 g; 95% CI -320, -4). This was no longer significant in children from 5 years of age (MD -160 g; 95% CI -580, 260). **Maheshwari 2012**: Systematic review and meta-analyses, including 11 studies of singleton pregnancies after the transfer of frozen thawed and fresh embryos generated through IVF. Compared with fresh embryos, frozen embryos were associated with lower risk for SGA (RR = 0.45, 95% CI 0.30–0.66), and LBW (RR = 0.69, 95% CI 0.62–0.76). **Sha 2018**: Meta-analysis, including 31 studies of 427,501 fresh-embryo cycles and 257,949 frozen-embryo cycles of IVF pregnancies. Pregnancies resulting from Frozen ET were associated with lower relative risks of placenta previa, placental abruption, low birth weight, very low birth weight, very preterm birth, small for gestational age, and perinatal mortality compared with fresh ET. Pregnancies occurring from Frozen ET were associated with increased risks of pregnancy-induced hypertension, postpartum hemorrhage, and large for gestational age compared with fresh ET.	after Frozen ET had a lower risk of LBW (aOR = 0.81, 95% CI 0.71–0.91) and SGA (SGA; aOR0.72, 95%CI 0.62–0.83) compared with singletons born after fresh ET. Compared with children conceived after spontaneous conception, singletons born after frozen ET had a higher risk of LBW (aOR = 1.27,95%CI 1.13–1.43), very LBW(aOR = 1.69, 95%CI 1.33–2.15), SGA (aOR = 1.18,95%CI 1.03–1.35) and LGA (aOR = 1.29, 95%CI 1.15–1.45)

Clinical question		
In pregnancies achieved via IVF, does low dose aspirin prophylaxis reduce the risk of fetal and placental complications?		
Recommendation statement		
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 - 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.		
Other organization recommendations		
USPSTF 2021: Systematic guideline. In vitro pregnancy is listed as a moderate risk factor for preeclampsia; recommend low-dose aspirin if patient has greater than or equal to 2 moderate risk factors; consider low-dose aspirin if patient has 1 moderate risk factor.		
Category A Evidence:	Category B Evidence:	Category C Evidence:
Groeneveld 2013: Meta-analysis of 268 IVF pregnancies, 131 treated with aspirin and 137 treated with placebo. There were no significant differences for hypertensive pregnancy complications: OR 0.62 (95% CI 0.22–1.7).	n/a	n/a

Clinical question
Is the prevalence of stillbirth increased in IVF pregnancies?

Recommendation statement		
Given the increased risk of stillbirth, we suggest weekly antenatal fetal surveillance beginning by 36 0/7 weeks of gestation for pregnancies achieved using IVF.		
GRADE		
2C - 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.		
Other organization recommendations		
ACOG CO 828: Non-systematic guideline. For pregnancies achieved using in vitro fertilization, weekly antenatal fetal surveillance may be considered beginning by 36 0/7 weeks of gestation.		
Category A Evidence:	Category B Evidence:	Category C Evidence:
n/a	**Jackson 2004**: Meta-analysis. 15 studies of 12,283 IVF and 1.9 million spontaneously conceived singletons. Compared with spontaneous conceptions, IVF singleton pregnancies were associated with significantly higher odds of perinatal mortality (odds ratio [OR] 2.2; 95% confidence interval [CI] 1.6, 3.0), preterm delivery (OR 2.0; 95% CI 1.7, 2.2), low birth weight (OR 1.8; 95% CI 1.4, 2.2), very low birth weight (OR 2.7; 95% CI 2.3, 3.1), and small for gestational age (OR 1.6; 95% CI 1.3, 2.0). Early preterm delivery, spontaneous preterm delivery, placenta previa, gestational diabetes, preeclampsia, and neonatal intensive care admission were also significantly more prevalent in the IVF group.	**Bay 2019:** Retrospective cohort study of 425,732 singleton pregnancies (10,235 via ICSI, 4521 via IUI, 410,976 via spontaneous conception). Rate of stillbirths: 0.3% among IVF/ICSI vs 0.1% among spontaneous. Risk of stillbirth in pregnancies following IVF/ICSI was increased (odds ratio 2.1, 95% CI 1.4–3.1). The risk of stillbirth was correspondingly increased in time-to-event analyses taking risk time for each fetus into account from gestational week 37 and onwards (hazard ratio 2.4, 95% CI 1.6–3.6). In sub-analyses, the risk of stillbirth was increased for pregnancies following ICSI (odds ratio 2.2, 95% CI 1.2–3.1), but not IVF (odds ratio 1.7, 95% CI 0.9–3.1).

	Sha 2018: Meta-analysis. 31 studies of 427,501 fresh-embryo cycles and 257,949 frozen-embryo cycles of IVF pregnancies. Pregnancies resulting from Frozen ET were associated with lower relative risks of placenta previa, placental abruption, low birth weight, very low birth weight, very preterm birth, small for gestational age, and perinatal mortality compared with fresh ET. Pregnancies occurring from Frozen ET were associated with increased risks of pregnancy-induced hypertension, postpartum hemorrhage, and large for gestational age compared with fresh ET.	**Marino 2014:** Retrospective cohort study of 327,378 births, including 321,210 spontaneous pregnancies. Relative to spontaneous conceptions, singletons from assisted conception were more likely to be stillborn (OR = 1.82, 95% Confidence Interval (CI) 1.34–2.48). Very low and low birth weight, very preterm and preterm birth, and neonatal death were markedly more common in singleton births from IVF and to a lesser degree, in births from ICSI. Using frozen-embryos eliminated all significant adverse outcomes associated with ICSI but not with IVF. **Wisborg 2010:** Prospective cohort study of 20,166 singleton pregnancies, including 879 conceived after non-IVF ART and 742 conceived after IVF/ICSI. The risk of stillbirth in women who conceived after IVF/ICSI was 16.2/1000, in women who conceived after non-IVF ART 2.3/1000. Compared with fertile women, women who conceived after IVF/ICSI had more than four times the risk of stillbirth [odds ratio (OR): 4.44, 95% confidence interval (CI): 2.38–8.28], and adjustments for maternal age, BMI, education, smoking habits and alcohol and coffee intake during pregnancy had only minor impact on the findings (OR: 4.08; 95% CI: 2.11–7.93).

Clinical question

In pregnancies achieved via IVF, does delivery at 39 weeks reduce the risk of adverse perinatal outcomes?		
Recommendation statement		
In the absence of studies focused specifically on timing of delivery for pregnancies achieved with IVF, we recommend shared decision-making between patients and health-care providers when considering induction of labor at 39 weeks of gestation.		
GRADE		
1C - Benefits appear 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.		
Other organization recommendations		
Lagrew 2018: Consensus bundle addressing safe reduction of primary cesarean births. The provision of maternity care during the prenatal, intrapartum, and postpartum periods offers a sustained opportunity for maternity care professionals to routinely engage women and families in education and informed and shared decision-making that can enhance opportunities for vaginal birth.		
Category A Evidence:	Category B Evidence:	Category C Evidence:
Saccone 2019: Systematic review and meta-analysis. 7 RCTs of 7598 participants comparing planned induction of labor between 39 0/7-39 6/7 weeks and expectant management until 41-42 weeks. Uncomplicated full-term singleton gestations that were randomized to receive induction of labor had similar incidence of cesarean delivery compared with controls (18.6% vs 21.4%; RR = 0.96, 95% CI 0.78-1.19).	n/a	**n/a**