

Pregnancy Outcomes After Assisted Reproductive Technology

This guideline has been reviewed by the Genetics Committee and the Reproductive Endocrinology and Infertility Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada and the Board of the Canadian Fertility and Andrology Society.

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Abstract

Objective: To review the effect of assisted reproductive technology (ART) on perinatal outcomes, to provide guidelines to optimize obstetrical management and counselling of Canadian women

Key Words: Assisted reproductive technology, pregnancy outcomes, multiple gestation, imprinting, congenital anomalies

using ART, and to identify areas specific to birth outcomes and ART requiring further research.

Options: Perinatal outcomes of ART pregnancies in subfertile women are compared with those of spontaneously conceived pregnancies. Perinatal outcomes are compared between different types of ART.

Outcomes: This guideline discusses the adverse outcomes that have been recorded in association with ART, including obstetrical complications, adverse perinatal outcomes, multiple gestations, structural congenital abnormalities, chromosomal abnormalities, imprinting disorders, and childhood cancer.

Evidence: The Cochrane Library and MEDLINE were searched for English-language articles from 1990 to February 2005, relating to assisted reproduction and perinatal outcomes. Search terms included assisted reproduction, assisted reproductive technology, ovulation induction, intracytoplasmic sperm injection (ICSI), embryo transfer, and in vitro fertilization (IVF). Additional publications were identified from the bibliographies of these articles as well as the Science Citation Index. Studies assessing gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT) were excluded since they are rarely used in Canada. All study types were reviewed. Randomized controlled trials were considered evidence of the highest quality, followed by cohort studies. Key studies and supporting data for each recommendation are summarized with evaluative comments and referenced.

Values: The evidence collected was reviewed by the Genetics Committee and the Reproductive Endocrinology Infertility Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) and quantified using the Evaluation of Evidence Guidelines developed by the Canadian Task Force on the Periodic Health Examination.

Benefits, harms, and costs: The type and magnitude of benefits, harms, and costs expected for patients from guideline implementation.

Recommendations:

1. Spontaneous pregnancies in untreated infertile women may be at higher risk for obstetrical complications and perinatal mortality than spontaneous pregnancies in fertile women. Further research is required to clarify the contribution of infertility itself to adverse obstetrical and perinatal outcomes. (II-2A)
2. All men with severe oligozoospermia or azoospermia should be offered genetic/clinical counselling for informed consent and offered karyotyping for chromosomal abnormalities before attempting IVF-ICSI. They should be made aware of the availability of tests for Y chromosome microdeletion. Some patients may consider the option of donor insemination. (II-3B)

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3. Couples exploring IVF-ICSI when the man has obstructive azoospermia should be offered genetic/clinical counselling for informed consent and offered genetic testing for alterations in genes associated with cystic fibrosis (CF) before attempting IVF-ICSI. (II-2A)
4. Pregnancies achieved by ovarian stimulation with gonadotropins and intrauterine insemination are at higher risk for perinatal complications, and close surveillance during pregnancy should be considered. It remains unclear if these increased risks are attributable to the underlying infertility, characteristics of the infertile couple, or use of assisted reproductive techniques. Multiple gestations remain a significant risk of gonadotropin treatment. (II-2A)
5. Pregnancies achieved by IVF with or without ICSI are at higher risk for obstetrical and perinatal complications than spontaneous pregnancies, and close surveillance during pregnancy should be considered. It remains unclear if these increased risks are attributable to the underlying infertility, characteristics of the infertile couple, or use of assisted reproductive techniques. (II-2A)
6. Women undergoing ART should be informed about the increased rate of obstetrical interventions such as induced labour and elective Caesarean delivery. (II-2A)
7. Couples suffering from infertility who are exploring treatment options should be made aware of the psychosocial implications of ART. Further research into the psychosocial impact of ART is needed. (II-2A)
8. Singleton pregnancies achieved by assisted reproduction are at higher risk than spontaneous pregnancies for adverse perinatal outcomes, including perinatal mortality, preterm delivery, and low birth weight, and close surveillance during pregnancy should be available as needed. (II-2A)
9. A significant risk of ART is multiple pregnancies. Infertile couples need to be informed of the increased risks of multifetal pregnancies. Although dichorionic twins are most common, the incidence of monozygotic twins is also increased. Risks of multiple pregnancies include higher rates of perinatal mortality, preterm birth, low birth weight, gestational hypertension, placental abruption, and placenta previa. Perinatal mortality in assisted conception twin pregnancies appears to be lower than in spontaneously conceived twin pregnancies. (II-2A)
10. When multifetal reduction is being considered for high-order multiple pregnancies, psychosocial counselling should be readily available. Careful surveillance for fetal growth problems should be undertaken after multifetal reduction. (II-2A)
11. To reduce the risks of multiple pregnancies associated with ART and to optimize pregnancy rates, national guidelines should be developed on the number of embryos replaced according to characteristics such as patient's age and grade of embryos. (II-2A)
12. Further epidemiologic and basic science research is needed to help determine the etiology and extent of the increased risks to childhood and long-term growth and development associated with ART. (II-2A)
13. Discussion of options for prenatal screening for congenital structural abnormalities in pregnancies achieved by ART is recommended, including appropriate use of biochemical and sonographic screening. (II-2A)
14. Further epidemiologic and basic science research is needed to help determine the etiology and extent of the increased risks of congenital abnormalities associated with ART. (II-2A)
15. Couples considering IVF-ICSI for male-factor infertility should receive information, and if necessary formal genetic counselling, about the increased risk of *de novo* chromosomal abnormalities (mainly sex chromosomal anomalies) associated with their condition. Prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis should be offered to these couples if they conceive. (II-2A)
16. Further epidemiologic and basic science research is needed to help determine the etiology and extent of the increased risks of chromosomal abnormalities associated with ART. (II-2A)
17. Discussion of options for prenatal screening and testing for aneuploidy in pregnancies achieved by ART, adapted for maternal age and number of fetuses, is recommended, including appropriate use of biochemical and sonographic screening. (II-2A)
18. The precise risks of imprinting and childhood cancer from ART remain unclear but cannot be ignored. Further clinical research, including long-term follow-up, is urgently required to evaluate the prevalence of imprinting disorders and cancers associated with ART. (II-2A)
19. The clinical application of preimplantation genetic diagnosis must balance the benefits of avoiding disease transmission with the medical risks and financial burden of in vitro fertilization. Further ethical discussion and clinical research is required to evaluate appropriate indications for preimplantation genetic diagnosis. (III-B)

Validation: These guidelines have been reviewed by the Genetics Committee and the Reproductive Endocrinology and Infertility Committee of the SOGC. Final approval has been given by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada and the Board of the Canadian Fertility and Andrology Society (CFAS).

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

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INTRODUCTION

Assisted reproductive technology (ART) involves handling eggs, sperm, or both outside the human body.

ART includes in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), fresh or frozen/thawed embryo transfer, IVF with donor oocytes, and intrauterine insemination either with ovarian stimulation using gonadotropins or oral medications such as clomiphene (OS-IUI) or in unstimulated cycles (IUI). Standard IVF involves the extracorporeal fertilization of sperm and eggs through spontaneous interaction, culture of embryos for 2 to 5 days, and transfer of embryo(s) into the uterus. Supernumerary embryos of good quality are cryopreserved and transferred into the uterus at a later date. ICSI is a microscopic procedure used to facilitate fertilization by injecting a single sperm directly into the oocyte. IVF with donor oocytes is a treatment for women with poor or no ovarian function (e.g., premature ovarian failure). Eggs obtained from a suitable donor are fertilized with sperm from the recipient's partner and the resulting embryos are transferred into the recipient's uterus. In OS-IUI, women receive gonadotropin injections to promote the maturation of multiple eggs. At the time of ovulation, the partner's sperm are prepared and then deposited into the uterine cavity using a small catheter.

The level and duration of regulation of these services varies considerably in different countries. For example, the Fertility Clinic Success Rate and Certification Act in the United

Table 1. Criteria for quality of evidence assessment and classification of recommendations

Level of evidence*	Classification of recommendations†
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.¹¹⁷

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.¹¹⁷

States requires the US Centers for Disease Control and Prevention (CDC) to publish clinic-specific pregnancy success rates for ART.¹ The European Society of Human Reproduction and Embryology (ESHRE) reports contributions from 22 countries to the European IVF-monitoring program.² In Canada, IVF clinic data are currently collected by the Canadian ART Registry (CARTR), and IVF clinics are currently accredited by the Canadian Council on Health Services Accreditation (CCHSA). Both were initiatives developed by the Canadian Fertility and Andrology Society (CFAS). With royal assent of Bill C6 (legislation to regulate the practice of ART in Canada) in 2004, the newly created Assisted Human Reproduction Agency of Canada (AHRAC) will assume the responsibilities of licensing, monitoring, inspection, and enforcement of regulations for ART clinics and developing a national reporting mechanism to collect information on ART outcomes.³

In recent years, an increasingly large proportion of deliveries following ART have been multiple pregnancies^{1,4-6} (Table 2). The most important reason for the increased rates of adverse perinatal outcomes observed in ART pregnancies is multifetal pregnancies. In addition, even in singleton pregnancies, ART may be associated with an increased risk of adverse perinatal outcomes, including increased rates of labour induction and Caesarean delivery. A small but significant increase in congenital structural anomalies and chromosomal abnormalities has also been observed in singleton ART pregnancies in studies including pregnancy terminations.⁷⁻¹¹ Case reports suggest an association between imprinting disorders and ART as well.¹²⁻¹⁸ Observed increases in risks of adverse outcomes may be secondary to

treatment or to the pathophysiology underlying the subfertility itself.

This guideline reviews the current data available on the outcomes of ART pregnancies according to the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Examination (Table 1). The Cochrane Library and MEDLINE were searched for English-language articles from 1990 to February 2005, relating to assisted reproduction and perinatal outcomes. Search terms included assisted reproduction, assisted reproductive technology, ovulation induction, intracytoplasmic sperm injection, embryo transfer, and in vitro fertilization. Additional publications were identified from the bibliographies of these articles as well as the Science Citation Index. Included studies were restricted to known IVF and IVF with ICSI treatments. Studies on gamete intrafallopian transfer (GIFT) or zygote intrafallopian transfer (ZIFT), alone or in combination with IVF treatment, were excluded, since they are rarely used in Canada. All study designs were reviewed. Well-conducted randomized controlled trials were considered evidence of the highest quality, followed by cohort studies. Key studies and supporting data for each recommendation are summarized with evaluative comments and referenced.

OUTCOMES ASSOCIATED WITH UNTREATED INFERTILITY

Infertility itself may increase the risk of adverse obstetrical and perinatal outcomes.¹⁹ Unadjusted analyses suggest a 2-fold increased risk of preeclampsia, placental abruption, Caesarean section, and vacuum extraction, and a 5-fold

Table 2. Percentage of deliveries in the United States, Europe, and Canada following ART by plurality

Country	Number of deliveries following ART	Singleton %	Twin %	Triplet and higher order pregnancy %
United States 2002 ¹	25 641	58	29	7*
Europe 2000 ⁴	34 392	74	24	2
Canada 2002 ⁶	2201†	68	29	3

Superscripts refer to reference numbers unless otherwise stated.

*US figures do not total 100%: 6% of pregnancies ended in miscarriage in which the number of fetuses could not be accurately determined.

†Number of ongoing pregnancies (pregnancy rate minus miscarriage rate).

ART: assisted reproductive technology.

increased risk of placenta previa in spontaneous singleton pregnancies in women with a history of infertility compared with the general population.²⁰ Analyses adjusted for age and parity suggest a 1.4 to 1.8-fold increase in risk for preterm delivery in women requiring greater than 1 year to spontaneously conceive singleton pregnancies, compared with women conceiving without delay.^{21,22} A 3-fold increased risk of perinatal mortality has been observed in women with untreated infertility²³ compared with women without infertility after adjusting for potential confounders.

Infertility is associated with abnormal sperm parameters in approximately 50% of the cases. Studies have shown that 4.6% of oligozoospermic men and 13.7% of azoospermic men have constitutional chromosomal abnormalities, the most common being sex chromosomal abnormalities and autosomal translocations.²⁴ As expected, infertile men with chromosomal abnormalities are more likely to have genetically abnormal spermatozoa and to father chromosomally abnormal pregnancies.²⁵ Microdeletions in the long arm of the Y chromosome were found in 6% of men with severe oligozoospermia (< 5 million/mL)^{26,27} that were significantly higher than normozoospermic controls (0.3%, $P < 0.001$).²⁶ In addition, obstructive azoospermia has been associated with mutations of the cystic fibrosis transmembrane regulator (CFTR) gene, with minor or incomplete forms of cystic fibrosis (CF) presenting either with congenital unilateral or congenital bilateral absence of the vas deferens (CBAVD) or without any structural abnormalities. Although aneuploidy is not increased in the sperm of these azoospermic men affected with a CFTR gene mutation, their IVF-ICSI offspring are at an increased risk for CF. Testing of men with CBAVD should include screening for CFTR mutations including the IVS8-5T allele. Since such screening may miss 11% of detectable CFTR gene mutations seen in males with CBAVD,²⁸ screening of the female partner is also recommended to provide more accurate information on the risk of having an affected child.²⁹ Genetic screening of men with less than 5 million spermatozoa per mL of semen has been recommended as routine by the World Health Organization since 2000.³⁰

Finally, the likelihood of sperm sex chromosomal abnormalities in karyotypically normal men (46,XY) has been significantly correlated with the severity of oligozoospermia.³¹

The indiscriminate use of ICSI should be discouraged, based on reports that fewer embryos are created per equal cohort of mature oocytes when ICSI is used instead of traditional IVF for cases where IVF was not specifically contraindicated.³² However, figures for this remain imprecise, being highly dependent on individual laboratories' performance, and each ART centre should establish its own specific guidelines.

Recommendations

1. Spontaneous pregnancies in untreated infertile women may be at higher risk for obstetrical complications and perinatal mortality than spontaneous pregnancies in fertile women. Further research is required to clarify the contribution of infertility itself to adverse obstetrical and perinatal outcomes. (II-2A)
2. All men with severe oligozoospermia or azoospermia should be offered genetic/clinical counselling for informed consent and offered karyotyping for chromosomal abnormalities before attempting IVF-ICSI. They should be made aware of the availability of tests for Y chromosome microdeletion. Some patients may consider the option of donor insemination. (II-3B)
3. Couples exploring IVF-ICSI when the man has obstructive azoospermia should be offered genetic/clinical counselling for informed consent and offered genetic testing for alterations in genes associated with CF before attempting IVF-ICSI. (II-2A)

OBSTETRICAL, PERINATAL, AND LONG-TERM OUTCOMES ASSOCIATED WITH ASSISTED REPRODUCTIVE TECHNOLOGY

Ovarian Stimulation

Limited information has linked intrauterine insemination and donor insemination to an increased incidence of preterm birth in singleton pregnancies after adjusting for

Table 3. Singleton pregnancy outcomes after superovulation–IUI compared with spontaneously conceived pregnancies (controlling for maternal age ± parity)

	Incidence in assisted conception %	Incidence in spontaneous conception %	Relative risk/ Odds ratio
Obstetrical Complications			
Gestational hypertension	1.1 ³⁶ , 11.3 ³⁴	0.7 ³⁶ , 8.6 ³⁴	1.8 ^{34*}
Placenta previa	0 ³⁶	0 ³⁶	
Placental abruption	0 ³⁶	0.4 ³⁶	
Induction of labour	22.8 ³⁶	21.0 ³⁶	1.1 ³⁶
Caesarean delivery	25.0 ³⁶	25.0 ³⁶	1.0 ³⁶
Perinatal outcomes			
Perinatal mortality (per 1000)	11.1 ³⁶	7.2 ³⁶	1.5 ³⁶ , 1.7 ^{35*}
Preterm delivery < 37 wk	8.7 ³⁶ , 15.5 ³⁴	5.1 ³⁶ , 6.9 ³⁴	1.3 ^{35*} , 1.7 ³⁶ , 2.2 ^{34*}
Low birth weight < 2500 g	8.7 ³⁶ , 22.7 ³⁴	6.2 ³⁶ , 7.1 ³⁴	1.4 ³⁶ , 1.5 ^{35*} , 3.2 ^{34*}
NICU admission	2.2 ³⁶ , 16.5 ³⁴	6.5 ³⁶ , 12.7 ³⁴	0.3 ³⁶ , 1.3 ³⁴

Superscripts refer to reference numbers unless otherwise stated. **P* < 0.05. IUI: intrauterine insemination; NICU: neonatal intensive care unit.

maternal age.³³ Ovarian stimulation with or without intrauterine insemination is a widely used treatment option for couples with mild male factor infertility, ovulatory dysfunction, mild endometriosis, or unexplained infertility. Studies evaluating the effect of ovarian stimulation with gonadotropins on perinatal outcomes, controlling for maternal age and parity, have demonstrated a 1- to 2-fold increased risk for preterm birth and a 1- to 3-fold increased risk for low birth weight in singletons compared with spontaneous conception³⁴⁻³⁶ (Table 3). No differences in the rate of congenital malformations have been demonstrated in pregnancies conceived with IUI (4.6%) compared with spontaneously conceived pregnancies (3.5%).³⁵ No studies have shown an association between childhood tumours and ovulation stimulating drugs.^{37,38} Multiple gestations remain a significant risk of gonadotropin and antiestrogen treatment.³⁴⁻³⁶

Recommendation

4. Pregnancies achieved by ovarian stimulation with gonadotropins and intrauterine insemination are at higher risk for perinatal complications, and close surveillance during pregnancy should be considered. It remains unclear if these increased risks are attributable to the underlying infertility, characteristics of the infertile couple, or use of assisted reproductive techniques. Multiple gestations remain a significant risk of gonadotropin treatment. (II-2A)

IVF With or Without ICSI

Numerous studies have evaluated the effect of ART on adverse pregnancy outcomes, many of which have been limited by type of control group and lack of data on potential confounding variables.³⁹⁻⁴³ Recently, cohort studies have controlled for maternal age and parity in singleton and twin pregnancies^{15,44-52} and have evaluated the effect of ART on obstetrical complications and perinatal outcomes.

Obstetrical Outcomes

Tables 4 and 5 summarize controlled comparisons of obstetrical complications in singletons and twins following ART and spontaneous conception. Rates of gestational hypertension (2-fold), gestational diabetes (2-fold), placenta previa (3- to 6-fold), and placental abruption (2-fold) are significantly increased in women conceiving singletons and twins with IVF and IVF-ICSI compared with spontaneous conceptions.^{44,45,47,52}

Compared with mothers of IVF-ICSI singletons, mothers of IVF twins are more likely to have gestational hypertension but not gestational diabetes, placenta previa, or premature rupture of membranes.^{39,40,53} Compared with mothers of spontaneously conceived twins and singletons, mothers of IVF-ICSI twins are 2 to 7 times more likely to require sick leave and hospitalization during pregnancy, although their morbidity during pregnancy is not higher.⁵³ Singleton pregnancies following oocyte donation may be more likely to be complicated by pregnancy-induced hypertension and gestational diabetes.⁵⁴

Table 4. Singleton pregnancy outcomes after IVF compared with spontaneously conceived pregnancies (controlling for maternal age ± parity)

	IVF			IVF-ICSI		
	Incidence in IVF conception %	Incidence in spontaneous conception %	Relative risk/ Odds ratio	Incidence in IVF-ICSI conception %	Incidence in spontaneous conception %	Relative risk / Odds ratio / <i>P</i>
Obstetrical Complications						
Gestational diabetes	6.8 ⁴⁴	4.7 ⁴⁴	2.0 ^{44*}			
Gestational hypertension	10.3 ⁴⁴	3.8 ⁴⁴	1.6 ^{44*}	9.4 ⁴⁷	7.2 ⁴⁷	1.3 ^{47*}
Placenta previa	2.4 ⁴⁴	0.9 ⁴⁴	2.9 ^{44*}	2.3 ⁴⁷	0.4 ⁴⁷	6.4 ^{47*}
Placental abruption				2.0 ⁴⁷	1.1 ⁴⁷	1.8 ^{47*}
Induction of labour	21.9 ⁴⁴	19.6 ⁴⁴	1.6 ^{44*}			
Caesarean delivery	26.7 ⁴⁴	19.5 ⁴⁴	1.5 ^{48*} , 2.1 ^{44*}	33.5 ⁴⁷	13.9 ⁴⁷	<i>P</i> < 0.01 ⁴⁷
Perinatal outcomes						
Perinatal mortality (per 1000)	12.4 ⁴⁸	8.0 ⁴⁸	1.7 ^{48*}			
Preterm delivery < 37 wk	11.4 ⁴⁸ , 11.5 ⁴⁴ , 13.1 ⁴⁶	5.3 ⁴⁴ , 6.1 ⁴⁸ , 9.3 ⁴⁶	1.4 ^{46*} , 2.0 ^{48*} , 2.0 ^{44*}	12.1 ⁴⁷	6.7 ⁴⁷	1.8 ^{47*}
Low birth weight < 2500 g	9.4 ⁴⁶ , 9.5 ⁴⁴	3.8 ⁴⁴ , 5.8 ⁴⁶	1.6 ^{46*} , 1.7 ^{48*} , 1.8 ^{44*}	10.9 ⁴⁷	5.3 ⁴⁷	<i>P</i> < 0.01 ⁴⁷
Very low birth weight < 1500 g	1.7 ⁴⁶ , 2.5 ⁴⁴	0.97 ⁴⁶ , 0.99 ⁴⁴	1.8 ^{46*} , 2.7 ^{44*} , 3.0 ^{48*}	3.2 ⁴⁷	1.1 ⁴⁷	<i>P</i> < 0.01 ⁴⁷
Small for gestational age < 10th percentile	14.6 ⁴⁴	8.9 ⁴⁴	1.4 ^{48*} , 1.6 ^{44*}			
NICU admission	17.8 ⁴⁴	7.8 ⁴⁴	1.3 ^{48*} , 1.6 ^{44*}			

Superscripts refer to reference numbers unless otherwise stated. **P* < 0.05. IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; NICU: neonatal intensive care unit.

Compared with spontaneous conception, singleton and twin pregnancies following IVF and IVF-ICSI have a 2-fold increased rate of induction of labour and Caesarean delivery.^{15,39,44,47,48,52} IVF-ICSI twin pregnancies are more likely to have Caesarean delivery than IVF-ICSI singleton pregnancies, a trend also seen in spontaneously conceived pregnancies.⁵⁶

Levels of parenting stress in singleton pregnancies are similar in first-time mothers who conceived spontaneously and after IVF.⁵⁶ However, compared with women with IVF singletons, mothers of IVF multiples were more likely to have a dysfunctional parent-child interaction and perception of child difficulty, and these differences were also observed when IVF multiples were compared with spontaneously conceived singletons.⁵⁶ Families of twins conceived after IVF or ovulation induction had similar parenting styles and maternal adjustment when compared with families of spontaneously conceived twins.⁵⁷ Mothers of ART multiples were less likely to work outside the home at 1 year post partum (44%) than mothers who conceived spontaneously and mothers with IVF singleton births (74%). No difference

was reported in the use of medical treatment for depression.⁵⁶

Recommendations

5. Pregnancies achieved by IVF with or without ICSI are at higher risk for obstetrical and perinatal complications than spontaneous pregnancies, and close surveillance during pregnancy should be considered. It remains unclear if these increased risks are attributable to the underlying infertility, characteristics of the infertile couple, or use of ART. (II-2A)
6. Women undergoing ART should be informed about the increased rate of obstetrical interventions such as induced labour and elective Caesarean delivery. (II-2A)
7. Couples suffering from infertility who are exploring treatment options should be made aware of the psychosocial implications of ART. Further research into the psychosocial impact of ART is needed. (II-2A)

Table 5. Twin pregnancy outcome after IVF compared with spontaneously conceived pregnancies (controlling for maternal age ± parity)

	IVF			IVF-ICSI		
	Incidence in assisted conception %	Incidence in spontaneous conception %	Relative risk / Odds ratio	Incidence in assisted conception %	Incidence in spontaneous conception %	Relative risk/ Odds ratio / <i>P</i>
Obstetrical Complications						
Gestational diabetes	5.4 ³⁹	5.4 ³⁹	1.0 ³⁹			
Gestational hypertension	10.7 ³⁹ , 16 ⁵² , 20 ⁴⁹	6.3 ³⁹ , 13 ⁵²	1.2 ⁴⁹ , 1.3 ⁵² , 1.7 ³⁹			0.8 ⁵⁵
Placenta previa	2.1 ⁵² , 3.6 ³⁹	0 ⁵² , 0.7 ³⁹	3.1 ^{52*}			
Placental abruption	1.8 ³⁹	0 ³⁹				
Premature rupture of membranes	5.4 ³⁹ , 16 ⁵² , 20 ⁴⁹	5.4 ³⁹ , 12 ⁵²	1.0 ³⁹ , 1.1 ⁴⁹ , 1.2 ⁵²			
Induction of labour	5.4 ³⁹	6.3 ³⁹	2.0 ³⁹			
Caesarean delivery	23 ⁵² , 76.8 ³⁹	16 ⁵² , 58.0 ³⁹	1.2 ^{48*} , 1.3 ^{52*} , 1.3 ^{39*}	52.9 ⁵⁵ , 69.8 ⁴⁷	42.7 ⁵³ , 52.0 ⁴⁵	1.1 ⁵⁵ , <i>P</i> < 0.01 ⁴⁷
Perinatal outcomes						
Perinatal mortality (per 1000)	23, 54 ³⁹	27 ³⁹ , 43.3 ⁴⁸	0.6 ^{48*} , 2.0 ³⁹	13 ⁵⁵	12 ⁵³	<i>P</i> > 0.05 ⁵⁵
Preterm delivery < 37 wk	50 ⁴⁸ , 54 ⁵² , 67.9 ³⁹	41.1 ³⁹ , 45 ⁵² , 45.6 ⁴⁸	1.1 ^{48*} , 1.3 ^{52*} , 1.7 ^{39*}	43.9 ⁵⁵	41.5 ⁵³	0.95 ⁵⁵
Low birth weight < 2500 g	58 ⁴⁹ , 68.4 ³⁹	50.9 ³⁹	1.0 ⁴⁸ , 1.3 ⁴⁹ , 1.4 ^{39*}	42.4 ⁵⁵ , 56.7 ⁴⁷	40.5 ⁵³ , 52.3 ⁴⁵	0.9 ^{55*} , <i>P</i> > 0.05 ⁴⁷
Very low birth weight < 1500 g	11 ⁴⁹ , 16.1 ³⁹	9.8 ³⁹	0.9 ⁴⁸ , 1.1 ⁴⁹ , 1.6 ³⁹	7.5 ⁴⁷ , 10.0 ⁵⁵	6.8 ⁵³ , 13.9 ⁴⁵	0.9 ⁵⁵ , <i>P</i> > 0.05 ⁴⁷
Small for gestational age < 10th percentile	5 ⁵² , 15 ⁴⁹ , 25 ³⁹	4, 36.6 ³⁹	0.7 ³⁹ , 1.0 ⁴⁹ , 1.3 ⁵² , 1.3 ⁴⁸			
NICU admission	36.8 ³⁹	24.6 ³⁹	1.1 ^{48*} , 1.5 ^{39*}	56.3 ⁵⁵	52.43 ⁵⁵	1.2 ^{55*}

Superscripts refer to reference numbers unless otherwise stated. **P* < 0.05. IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; NICU: neonatal intensive care unit.

Perinatal Outcomes

Singleton birth

Table 4 summarizes controlled comparisons of perinatal outcomes in singletons following ART and spontaneous conception. Compared with spontaneous conceptions, IVF and IVF-ICSI singleton pregnancies are at increased risk for stillbirth or neonatal death (2-fold), preterm delivery (< 37 weeks, 1- to 2-fold), low birth weight (< 2500 g, 2-fold), very low birth weight (< 1500 g, 2- to 3-fold), small for gestational age (< 10th percentile birth weight for gestational age, 1- to 2-fold) and NICU admission (1- to 2-fold).^{35,44,46-49,58}

There is evidence that the risks for term low birth weight (but not preterm low birth weight) may be declining in singleton pregnancies after assisted reproduction.^{46,59} This trend may in part reflect a change in obstetric practice, such as closer monitoring and intervention before term for pregnancies with evidence of fetal growth restriction.⁶⁰

Recommendation

8. Singleton pregnancies achieved by assisted reproduction are at higher risk than spontaneous pregnancies for adverse outcomes, including perinatal mortality, preterm delivery, and low birth weight, and close surveillance during pregnancy should be available as needed. (II-2A)

Multiple birth

Although the number of multiple births has risen dramatically and may be associated with increasing maternal age, the majority of this increase in multiple births is due to the growing use of ART and transfer of multiple embryos.^{61,62} Multifetal pregnancy is one of the most important public health concerns associated with ART⁵¹ and is almost entirely attributable to the transfer of more than 1 embryo per treatment cycle. Interestingly, the proportion of monozygotic twins from IVF pregnancies is 1% to 2% at first ultrasound, compared with approximately 0.4% of live births from spontaneously conceived pregnancies.^{63,64} IVF pregnancies that occur after transferring blastocyst (5 days

after fertilization) embryos are more often associated with monozygotic twinning (6%) than pregnancies that occur after transferring cleavage-stage (2–3 days after fertilization) embryos (2%).^{53,63-65}

The risk of morbidity and mortality increases with each additional fetus in a multiple gestation,⁶⁶ and the medical cost per twin pregnancy has been reported as more than 5 times higher than per singleton pregnancy after IVF.⁶⁷ For example, to limit the incidence of multiple pregnancy, and particularly higher order multiple pregnancies, the Society of Assisted Reproductive Technology (SART) and the American Society of Reproductive Medicine (ASRM) have established guidelines for the number of embryos to be transferred during a single cycle of infertility treatment.⁶⁸ Several Northern European centres have demonstrated the efficacy of elective single embryo transfer (eSET) in reducing the incidence of multiple pregnancies while maintaining acceptable overall pregnancy rates in patients with good prognoses.² Guidelines should soon be developed in Canada to reduce the risks of multiple births from ART treatment.³ There appears to be no difference in the pregnancy rate between elective transfers with 2 (22.0%) and 3 embryos (22.5%, $P > 0.05$) in women up to the age of 40 years.⁶⁹

Table 5 summarizes controlled comparisons of perinatal outcomes of twins from ART and those of twins from spontaneous conception. A recent systematic review has demonstrated that twin pregnancies from assisted conception have a 40% lower perinatal mortality but a 1- to 2-fold increased risk of preterm delivery compared with twin pregnancies from spontaneous conception.⁴⁸ Controlled studies demonstrate conflicting results regarding the risks for preterm delivery, low birth weight, and small for gestational age,^{48,49,53,58} especially when only dizygotic twins are considered.⁵³ There is no difference in these perinatal outcomes between twin pregnancies from IVF-ICSI and those from standard IVF.⁷⁰

Multiple births generate significant physical, economic, and psychosocial costs. Fetal reduction for high-order multiple pregnancies is a very difficult decision for couples who have gone through fertility treatment, particularly when the procedure may result in loss of the entire pregnancy.⁷¹ Even when successful, fetal reduction may have long-term adverse emotional consequences for the couple.⁷²⁻⁷⁵ Compared with spontaneously conceived twin pregnancies, twin pregnancies remaining after fetal reduction have a 3- to 4-fold increase in low birth weight, very low birth weight, and fetal growth restriction.⁴⁹ Fetal growth restriction consequent to fetal reduction might represent placental insufficiency⁷⁶ or be the result of abnormal implantation of the higher number of embryos. In addition, residual placental

tissue from the reduced fetuses may promote a subclinical inflammatory response leading to preterm birth.⁷⁷

Recommendations

9. A significant risk of ART is multiple pregnancies. Infertile couples need to be informed of the increased risks of multifetal pregnancies. Although dichorionic twins are most common, the incidence of monochorionic twins is also increased. Risks of multiple pregnancies include higher rates of perinatal mortality, preterm birth, low birth weight, gestational hypertension, placental abruption, and placenta previa. Perinatal mortality in assisted conception twin pregnancies appears to be lower than in spontaneously conceived twin pregnancies. (II-2A)
10. When multifetal reduction is being considered for high-order multiple pregnancies, psychosocial counseling should be readily available. Careful surveillance for fetal growth problems should be undertaken after multifetal reduction. (II-2A)
11. To reduce the risks of multiple pregnancies associated with ART and to optimize pregnancy rates, national guidelines should be developed on the number of embryos replaced according to characteristics such as patient's age and grade of embryos. (II-2A)

Long-Term Outcomes

Preliminary data suggest that singleton babies conceived with IVF-ICSI may have a 1.6-fold risk of slower postnatal growth in the first 3 years of life⁵⁰ compared with spontaneously conceived singletons, but not at 5 years of age.⁷⁸ Interestingly, these growth discrepancies have not been observed among IVF, IVF-ICSI, and spontaneously conceived twins.^{15,50}

In a 5-year follow-up study, IVF and IVF-ICSI children were more likely than spontaneously conceived (SC) children to have had a significant childhood illness (74% ICSI, 77% IVF, 57% SC, $P < 0.001$), to have had a surgical operation (24% ICSI, 22% IVF, 14% SC, $P < 0.001$), to require medical therapies (11% ICSI, 9% IVF, 5% SC, $P < 0.001$), and to be admitted to hospital (31% ICSI, 28% IVF, 20% SC, $P < 0.001$).⁷⁹ In 2- and 5-year follow-up studies, there did not appear to be any differences in psychomotor, cognitive, intellectual, or psychological development between IVF, IVF-ICSI, and spontaneously conceived children.^{15,78,80-82}

Recommendation

12. Further epidemiologic and basic science research is needed to help determine the etiology and extent of the increased risks to childhood and long-term growth and development associated with ART. (II-2A)

Table 6. Structural congenital abnormalities in births and pregnancies terminated for congenital anomalies in IVF compared with spontaneously conceived pregnancies

Structural abnormality	IVF			IVF-ICSI		
	Incidence in IVF conception %	Incidence in spontaneous conception %	<i>P</i>	Incidence in IVF-ICSI conception %	Incidence in spontaneous conception %	Relative risk / Odds ratio / <i>P</i>
Any major malformation*	9.0 ⁹²	4.2 ⁹²	< 0.001 ⁹²	8.6 ⁹² , 8.8 ⁴⁷	4.2 ⁹² , 6.1 ⁴⁷	< 0.001 ⁹² , 1.4 ^{47**}
Cardiovascular	1.8 ⁹²	0.6 ⁹²	< 0.001 ⁹²	1.3 ⁹² , 2.1 ⁴⁷	0.6 ⁹² , 1.4 ⁴⁷	> 0.05 ⁹² , 1.5 ^{47**}
Gastrointestinal	0.6 ⁹²	0.6 ⁹²	> 0.05 ⁹²	0.7 ⁴⁷ , 1.0 ⁹²	0.3 ⁴⁷ , 0.6 ⁹²	> 0.05 ⁹² , 2.6 ^{47**}
Urogenital	2.6 ⁹²	1.4 ⁹²	0.01 ⁹²	2.3 ⁹² , 3.2 ⁴⁷	1.4 ⁹² , 1.5 ⁴⁷	> 0.05 ⁹² , 2.2 ⁴⁷
Musculoskeletal	3.3 ⁹²	1.1 ⁹²	< 0.001 ⁹²	1.8 ⁴⁷ , 3.3 ⁹²	1.1 ⁹² , 1.8 ⁴⁷	0.004 ⁹² , 1.0 ⁴⁷
Central nervous system	0.4 ⁹²	0.2 ⁹²	> 0.05 ⁹²	0 ⁹² , 0.6 ⁴⁷	0.2 ⁹² , 0.6 ⁴⁷	1.0 ⁴⁷

*As defined by the respective birth registries. Superscripts refer to reference numbers unless otherwise stated. ***P* < 0.05. IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; NICU: neonatal intensive care unit.

GENETIC AND STRUCTURAL ABNORMALITIES ASSOCIATED WITH ASSISTED REPRODUCTIVE TECHNOLOGY

Structural Congenital Abnormalities

Evaluation of the association between ART and structural congenital abnormalities has been limited by small sample size in case reports and case series, varying definitions of congenital anomalies, and lack of data on potential confounding variables.^{8,83-91} Registry data demonstrated a 2-fold increased risk for major congenital abnormalities in both singletons and twins following IVF (9.0%) and IVF-ICSI (8.6%) that was significantly increased compared with spontaneous conceptions (4.2%) after adjusting for maternal age and parity or ethnicity and including pregnancies terminated for congenital anomalies⁹² (Table 6). IVF-ICSI has been shown to have a 2-fold increased risk for major malformations in singletons (8.9%) compared with spontaneous conceptions (6.0%) in tertiary centres, and a 2-fold risk for major malformations in twins following IVF-ICSI compared with singletons following IVF-ICSI.^{47,93}

Recommendations

- Discussion of options for prenatal screening for congenital structural abnormalities in pregnancies achieved by ART is recommended, including appropriate use of biochemical and sonographic screening. (II-2A)
- Further epidemiologic and basic science research is needed to help determine the etiology and extent of the increased risks of congenital abnormalities associated with ART. (II-2A)

Chromosomal Disorders

The incidence of any chromosomal abnormality in births and induced terminations, after adjusting for maternal age and parity, following IVF (0.7%) has been shown to be similar to spontaneously conceived pregnancies (0.2%), but significantly higher following IVF-ICSI (1.0%).⁹³ Significantly more *de novo* chromosomal aberrations have been diagnosed prenatally in children conceived by IVF-ICSI compared with the general newborn population,⁹⁴ which may be related to a higher number of sex chromosomal aberrations in the offspring of oligozoospermic men, even those with a normal karyotype.^{29,94-97}

Recommendations

- Couples considering IVF-ICSI for male-factor infertility should receive information, and if necessary formal genetic counselling, about the increased risk of *de novo* chromosomal abnormalities (mainly sex chromosomal anomalies) associated with their condition. Prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis should be offered to these couples if they conceive. (II-2A)
- Further epidemiologic and basic science research is needed to help determine the etiology and extent of the increased risks of chromosomal abnormalities associated with ART. (II-2A)

Prenatal Diagnosis of Structural and Chromosomal Abnormalities

Options for prenatal diagnosis of aneuploidy in patients who conceive from ART are primarily determined by their maternal age, except for those who conceive from IVF-ICSI, because of an increased risk of aneuploidy associated with ICSI independent of maternal age. No

differences have been observed in the values for maternal serum markers or nuchal translucency measurements in IVF and IVF-ICSI pregnancies compared with spontaneously conceived pregnancies.^{98,99} Increased maternal serum alpha-fetoprotein (MSAFP) is not a reliable marker for neural tube defects following fetal reduction.¹⁰⁰ Elevated MSAFP levels have been observed in pregnancies conceived with donor oocytes.¹⁰¹

For North American women offered invasive prenatal testing for aneuploidy, no differences were observed in the acceptance rate of genetic amniocentesis among women with IVF pregnancies compared with those who conceive spontaneously, and this was not influenced by the presence of multiple gestations.¹⁰²

Recommendation

17. Discussion of options for prenatal screening and testing for aneuploidy in pregnancies achieved by ART, adapted for maternal age and number of fetuses, is recommended, including appropriate use of biochemical and sonographic screening. (II-2A)

Imprinting Disorders

Some evidence suggests a link between ART and epigenetic alterations, which include DNA modifications such as methylation and genomic imprinting problems.^{103,104} A number of genes regulated by imprinting have been shown to be essential to fetal growth and placental function.¹⁰⁵

Two genetic imprinting disorders involving birth defects have recently been associated with ART: Beckwith-Wiedemann syndrome (BWS)¹²⁻¹⁵ and Angelman's syndrome.^{16,17} BWS is characterized by prenatal overgrowth, abdominal wall defects (omphalocele or umbilical hernia), neonatal hypoglycemia, hemihypertrophy, ear abnormalities, and macroglossia. Children with BWS are at increased risk of developing embryonal tumours, including Wilms tumour and hepatoblastoma. Children born with BWS are 18 times more likely to have been conceived from IVF treatment than children without BWS.¹⁵ However, the risk of BWS in an IVF population is still rare at 1/4000 children.¹⁰⁶ Angelman's syndrome, another rare imprinting disorder, is characterized by severe developmental delay, absent speech, seizures, ataxia, hyperreflexia, and hypotonia.¹⁰⁷ Further, existing studies have been limited by reliance on case records or questionnaire data, lack of use of appropriate controls, and sample size. It is unclear whether the higher incidence of epigenetic alterations after ART arises as a result of in vitro culture procedure itself, the culture media used, or medications used to stimulate the ovaries. Epigenetic problems might also be a cause of infertility,

with infertile couples having an increased prevalence of epigenetic defects present in their gametes.¹⁰⁸

Independent of congenital genetic syndromes, epigenetics may also play a critical role in human cancer. Alterations in DNA methylation are linked to disrupted gene expression in a wide variety of tumours. Loss of imprinting is also common in both childhood and adult tumours, and loss of imprinting in normal cells has recently been linked to an increased personal and family history of colorectal cancer.¹⁰⁴ Retinoblastoma has a frequency of 1:17 000 in the general population. Although 1 study demonstrated a 5- to 7-fold increased risk of retinoblastoma following ART,¹⁸ other studies have demonstrated no association between ART and retinoblastoma and other childhood cancers.^{37,38,109,110} Further, in a 1-year follow-up study, spontaneously conceived twins were more likely to develop childhood cancer than IVF twins.⁵³

Recommendation

18. The precise risks of imprinting and childhood cancer from ART remain unclear but cannot be ignored. Further clinical research, including long-term follow-up, is urgently required to evaluate the prevalence of imprinting disorders and cancers associated with ART. (II-2A)

Preimplantation Genetic Diagnosis

Preimplantation genetic diagnosis (PGD) is a tool in IVF with or without ICSI that allows early cleavage-stage embryos to be tested for chromosomal aneuploidy and genetic defects (such as hemophilia, CF, and Tay-Sachs) before transfer. Embryo biopsy for PGD is typically performed on the third day of early embryonic development after IVF with or without ICSI, although some ART centres are now performing PGD routinely on blastocysts at day 5.^{111,112} PGD is an important option for families who do not wish to pursue the strategy of testing during pregnancy followed by elective abortion of the abnormal fetus.^{113,114}

Clinical guidelines for PGD have been developed by the ESHRE Consortium.¹¹⁵ All couples whose offspring are at high genetic risk because of structural chromosome abnormalities or monogenic diseases should be offered non-directive genetic counselling by a specialist in genetics. Reproductive options and alternatives to PGD such as prenatal diagnosis, no testing, adoption, or gamete donation should be reviewed. The reliability of PGD, along with information on the significance and limitations of the diagnostic test, should be discussed with the couple. The risk of misdiagnosis (0.9–2% for fluorescence in situ hybridization [FISH] and 8–9% for polymerase chain reaction [PCR])¹¹⁶ and non-informative results should be covered, including the option of prenatal testing to complete or confirm the PGD results. The couple should be informed of the potential effects of PGD and ART treatments on the pregnancy

and the child. Finally, the couple should have treatment-specific counselling with members of the fertility centre.¹¹⁵

Recommendation

19. The clinical application of preimplantation genetic diagnosis must balance the benefits of avoiding disease transmission with the medical risks and financial burden of IVF. Further ethical discussion and clinical research is required to evaluate appropriate indications for PGD. (III-B)

LIMITATIONS OF STUDIES

The major methodological problem in many of the studies evaluating the effect of ART involves the comparison of outcomes in pregnancies achieved following treatment in subfertile women with outcomes following spontaneous conception in fertile women or in the general population. Fundamental differences in patient characteristics may confound the results and make it difficult to distinguish the effects of ART treatment from the underlying disease. Well-designed studies in subfertile women comparing the risks in ART treated pregnancies with the risks in spontaneous pregnancies are required.

A number of other methodological issues affect the evaluation of the relationship between adverse obstetrical and perinatal outcomes and assisted human reproduction. A review of the evidence demonstrates limitations in these studies such as retrospective and non-standardized data collection, a paucity of information on potential confounding factors (such as maternal age and parity and pregnancy complications related to adverse outcomes), and small sample size. Control groups may have included infertile women who subsequently conceived spontaneously or with use of ovulation induction. Biases include treatment bias (patterns of obstetrical practice such as induction of labour or elective Caesarean delivery), reporting bias, and ascertainment bias. Several well-designed meta-analyses considering obstetrical and perinatal outcomes support increased risks for adverse outcomes associated with ART. Although careful appraisals of outcomes associated with ART are now increasing in quality and number, structured, prospective, and comprehensive data collection remains important.

SUMMARY

The majority of ART pregnancies are uncomplicated and result in the birth of healthy children. However, it is also clear that a higher proportion of ART pregnancies are associated with obstetrical and perinatal complications and that children conceived through ART may have a higher risk of abnormalities than spontaneously conceived children.

The majority of obstetric and pediatric problems after ART arise as a result of multiple pregnancies. National guidelines

need to be developed to reduce the number of embryos transferred in any single cycle to balance the risk of multiple pregnancies with the maintenance of acceptable overall pregnancy rates. It should be noted that limiting the number of embryos transferred per cycle will not reduce the proportion of multiple pregnancies resulting from superovulation and intrauterine insemination.

Even singleton ART pregnancies in subfertile women are associated with an increased risk of perinatal complications, congenital abnormalities, and possibly later childhood developmental problems than naturally conceived children of fertile women. The precise etiology of these specific problems has not yet been elucidated. However, couples considering ART need to know these risks. Furthermore, karyotyping of the male partner should always be offered prior to IVF-ICSI when severe oligozoospermia or non-obstructive azoospermia are identified. When azoospermia is thought to be due to CBAVD, genetic screening for CF should be offered before IVF-ICSI treatment. Genetic counselling and prenatal diagnosis should be offered to all couples who have successfully achieved a pregnancy from IVF-ICSI. It is hoped that the new legislation in Canada (Bill C6) will help regulate the standardized collection of ART surveillance data and that federal funding and infrastructure support will be available for the long-term follow-up of this cohort of children on the basis of this evidence, so that more can be learned about the outcome of ART pregnancies. Further research with well-constructed prospective, nationally regulated data collection, accounting for important confounding variables and minimizing bias, is needed to help determine the factors that might lead to the higher rates of problems observed with ART pregnancies. Such factors may include infertility itself, parental characteristics, ovarian stimulation, ICSI, or in vitro culture of embryos. It is imperative that the goal of ART remains the birth of healthy singleton babies rather than an increase in pregnancy rates alone. This clinical practice guideline requires ongoing evaluation of evolving evidence regarding the effects of ART to optimize patient care and outcomes.

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