

# Pregnancy Outcomes After Assisted Human Reproduction

This clinical practice guideline has been prepared by the Genetics Committee, reviewed by the Reproductive Endocrinology and Infertility Committee and the Family Physicians Advisory Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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**Key Words:** Assisted human reproduction, assisted reproductive technology, pregnancy outcomes, multiple gestation, imprinting, congenital anomalies, imprinting disorders.

## Abstract

**Objective:** To review the effect of assisted human reproduction (AHR) on perinatal outcomes, to identify areas requiring further research with regard to birth outcomes and AHR, and to provide guidelines to optimize obstetrical management and counselling of prospective Canadian parents.

**Outcomes:** This document compares perinatal outcomes of different types of AHR pregnancies with each other and with those of spontaneously conceived pregnancies. Clinicians will be better informed about the adverse outcomes that have been documented in association with AHR, including obstetrical complications, adverse perinatal outcomes, multiple gestations, structural congenital abnormalities, chromosomal abnormalities, and imprinting disorders.

**Evidence:** Published literature was retrieved through searches of MEDLINE and the Cochrane Library from January 2005 to December 2012 using appropriate controlled vocabulary and key words (assisted reproduction, assisted reproductive technology, ovulation induction, intracytoplasmic sperm injection, embryo transfer, and in vitro fertilization). Results were not restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies; studies of all designs published in English from January 2005 to December 2012 were reviewed, and additional publications were identified from the bibliographies of these articles. Searches were updated on a regular basis and incorporated in the guideline to August 2013. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

**Values:** The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

## Summary Statements

1. There is increasing evidence that infertility or subfertility is an independent risk factor for obstetrical complications and adverse perinatal outcomes, even without the addition of assisted human reproduction. (II-2)
2. The relative risk for an imprinting phenotype such as Silver-Russell syndrome, Beckwith-Wiedemann syndrome, or Angelman syndrome is increased in the assisted reproduction population, but the actual risk for one of these phenotypes to occur in an assisted

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**Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care**

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in 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 recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

\*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.<sup>176</sup>

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.<sup>176</sup>

pregnancy is estimated to be low, at less than 1 in 5000. The exact biological etiology for this increased imprinting risk is likely heterogeneous and requires more research. (II-2)

## Recommendations

- All men with severe oligozoospermia or azoospermia (sperm count < 5 million/hpf) should be offered genetic/clinical counselling, karyotype assessment for chromosomal abnormalities, and Y-chromosome microdeletion testing prior to in vitro fertilization with intracytoplasmic sperm injection. (II-2A)
- All men with unexplained obstructive azoospermia should be offered genetic/clinical counselling and genetic testing for cystic fibrosis prior to in vitro fertilization with intracytoplasmic sperm injection. (II-2A)
- Multiple pregnancy is the most powerful predictive factor for adverse maternal, obstetrical, and perinatal outcomes. Couples should be thoroughly counselled about the significant risks of multiple pregnancies associated with all assisted human reproductive treatments. (II-2A)
- The benefits and cumulative pregnancy rates of elective single embryo transfer support a policy of using this protocol in couples with good prognosis for success, and elective single embryo transfer should be strongly encouraged in this population. (II-2A)
- To reduce the incidence of multiple pregnancy, health care policies that support public funding for assisted human reproduction, with regulations promoting best practice regarding elective single embryo transfer, should be strongly encouraged. (II-2A)
- Among singleton pregnancies, assisted reproductive technology is associated with increased risks of preterm birth and low birth weight infants, and ovulation induction is associated with an increased risk of low birth weight infants. Until sufficient research has clarified the independent roles of infertility and treatment for infertility, couples should be counselled about the risks associated with treatment. (II-2B) There is a role for closer obstetric surveillance of women who conceive with assisted human reproduction. (III-L)
- There is growing evidence that pregnancy outcomes are better for cryopreserved embryos fertilized in vitro than for fresh embryo transfers. This finding supports a policy of elective single embryo transfer for women with a good prognosis (with subsequent use of cryopreserved embryos as necessary), and may reassure women who are considering in vitro fertilization. (II-2A)
- Women and couples considering assisted human reproduction and concerned about perinatal outcomes in singleton pregnancies should be advised that (1) intracytoplasmic sperm injection does not appear to confer increased adverse perinatal or maternal risk over standard in vitro fertilization, and (2) the use of donor oocytes increases successful pregnancy rates in selected women, but even when accounting for maternal age, can increase the risks of low birth weight and preeclampsia. (II-2B)
- Any assisted reproductive technology procedure should be prefaced by a discussion of fetal outcomes and the slight increase in the risk of congenital structural abnormalities, with emphasis on known confounding factors such as infertility and body mass index. (II-2B)
- In pregnancies achieved by artificial reproductive technology, routine anatomic ultrasound for congenital structural abnormalities is recommended between 18 and 22 weeks. (II-2A)
- Pregnancies conceived by intracytoplasmic sperm injection may be at increased risk of chromosomal aberrations, including sex chromosome abnormalities. Diagnostic testing should be offered after appropriate counselling. (II-2A)
- The possible increased risk for late onset cancer due to gene dysregulation for tumour suppression requires more long-term follow-up before the true risk can be determined. (III-A)
- The clinical application of preimplantation genetic testing in fertile couples must balance the benefits of avoiding disease transmission with the medical risks and financial burden of in vitro fertilization. (III-B)
- Preimplantation screening for aneuploidy is associated with inconsistent findings for improving pregnancy outcomes. Any discussion of preimplantation genetic screening with patients should clarify that there is no adequate information on the long-term effect of embryo single cell biopsy. (I-C)

## INTRODUCTION

Although the definition varies, assisted reproductive technology is commonly defined as any procedure that involves handling eggs, sperm, or both outside the human body (in vitro). ART includes in vitro fertilization, with or without intracytoplasmic sperm injection, with fresh or frozen embryos (by cryopreservation or by vitrification and thawed embryo transfer) and IVF with donor oocytes, gamete intrafallopian transfer, zygote intrafallopian transfer, and assisted zona hatching. ART has expanded to include not only in vitro procedures, but also intrauterine insemination and OS with gonadotropin or ovarian stimulating medications<sup>1</sup>

ART accounts for 1.7% to 4% of pregnancies<sup>2</sup> and has traditionally been used to address primary or secondary infertility.<sup>3</sup> More recently, its use has expanded to allow

## ABBREVIATIONS

AHR	assisted human reproduction
AHRC	Assisted Human Reproduction Canada
aOR	adjusted odds ratio
ART	assisted reproductive technology
ASRM	American Society for Reproductive Medicine
CARTR	Canadian Assisted Reproductive Technologies Registry
CBAVD	congenital bilateral absence of vas deferens
CFAS	Canadian Fertility and Andrology Society
DET	double embryo transfer
eSET	elective single embryo transfer
ESHRE	European Society of Human Reproduction and Embryology
ET	embryo transfer
FET	frozen embryo transfer
HFEA	Human Fertilisation and Embryology Authority
HR	hazard ratio
ISCI	intracytoplasmic sperm injection
IUI	intrauterine insemination
IVF	in vitro fertilization
LBW	low birth weight
MSAFP	maternal serum alpha-fetoprotein
PAPP-A	pregnancy-associated plasma protein-A
PGS	preimplantation genetic screening
RR	relative risk
OH	ovarian hyperstimulation
OI	ovulation induction
OS	ovarian stimulation
SART	Society for Assisted Reproduction Technologies
SGA	small for gestational age
TTP	time to pregnancy

fertility preservation after gonadotoxic treatments in reproductive-age patients,<sup>4,5</sup> to enable same-sex couples and single women and men to conceive and have biological children,<sup>6</sup> and to facilitate the services of surrogate gestational carriers.<sup>7</sup> The ethical and philosophical issues involved in AHR are complex and are handled differently in different countries, resulting in varying levels of regulation of these services.<sup>8–12</sup>

In Canada, the Assisted Human Reproduction Act,<sup>13</sup> which covers topics including allowed (surrogacy, gamete donation) and prohibited (human cloning, buying or selling human reproductive material) processes, led to the creation of Assisted Human Reproduction Canada, an agency responsible for the licensing, monitoring, inspection, and enforcement of regulations for ART clinics. Following a 2010 Supreme Court decision resulting from a Charter challenge from Quebec, aspects of the Act relating to prohibitions (sex selection, selling of human reproductive material) have remained within the Federal Act, but much of the regulation of ART services will fall back under provincial jurisdiction.<sup>14</sup> The 2012 Federal budget ordered the dissolution of AHRC in 2013, with its responsibilities redirected to Health Canada.<sup>4</sup>

Data for IVF clinics have been reported by the Canadian Assisted Reproductive Technologies Registry since 1999, under the auspices of the Canadian Fertility and Andrology Society.<sup>15</sup> IVF clinics are accredited by Accreditation Canada.<sup>16</sup>

The availability of treatment for infertility and subfertility (a term generally used to name any grade of reduced fertility in couples unsuccessfully trying to conceive<sup>17</sup>) is important to the family health of Canadians.<sup>18</sup> Obstetrical outcome data from pregnancies conceived by AHR and some long-term follow-up data on offspring suggest increased adverse outcomes related to AHR techniques. Care providers and prospective parents should be aware of these potential adverse outcomes.

This guideline reviews the outcome data of AHR pregnancies using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Examination (Table 1). We searched the Cochrane Library and Ovid MEDLINE for English-language articles related to assisted reproduction and perinatal outcomes published from February 2005 to December 2012 (overlapping with the previous SOGC guideline). 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 referenced and summarized with evaluative comments.

## OUTCOMES ASSOCIATED WITH UNTREATED INFERTILITY

Infertility, generally considered to be the inability to conceive after one year of attempting pregnancy,<sup>19</sup> has been identified as a significant independent predictor of adverse obstetrical and perinatal outcomes.<sup>20–22</sup> Unadjusted analyses suggest a 2-fold increased risk of preeclampsia, placental abruption, Caesarean section, and vacuum extraction, and a 5-fold increased risk of placenta previa in spontaneous singleton pregnancies in women with a history of infertility compared with women in the general population.<sup>23</sup>

Table 2 summarizes a number of studies documenting adjusted obstetrical, perinatal, and neonatal risks in populations of women with infertility or subfertility compared with control women.<sup>13,23–29</sup> Some of these studies compared women with various delays in time to pregnancy who eventually conceived spontaneously to populations of women with short TTP, and found significant differences in a number of adverse outcomes, including preterm birth, LBW, and perinatal mortality. Other studies compared populations of women with delays in TTP with and without ART and found insignificant differences between these 2 groups, but increases in adverse outcomes between these 2 groups and a control group of women with no delay in TTP.<sup>30,31</sup>

Maternal factors related to an increased risk of infertility also have an independently associated risk of adverse obstetrical outcomes. Advancing maternal age is associated with both declining fertility and multiple adverse outcomes of ongoing pregnancy, as noted recently in an SOGC committee opinion on delayed childbearing.<sup>32</sup> Research shows obesity impairs fertility,<sup>33,34</sup> although whether this effect is primarily ovarian or endometrial is controversial.<sup>35–37</sup> Obesity is also independently related to adverse obstetrical outcomes, many of them similar to those associated with advancing maternal age<sup>38</sup> and overlapping with those associated with AHR.

Although there is little remaining debate about the association of infertility or subfertility with adverse obstetrical outcomes following AHR, more specific associations between ovarian/ovum or testicular/sperm factors, endometrial factors, or other factors and adverse outcomes are not well understood.

### Summary Statement

1. There is increasing evidence that infertility or subfertility is an independent risk factor for obstetrical complications and adverse perinatal outcomes, even without the addition of assisted human reproduction. (II-2)

## OUTCOMES ASSOCIATED WITH MALE FACTOR INFERTILITY

Infertility is associated with male factor or abnormal sperm parameters in approximately 50% of cases.<sup>39</sup> 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.<sup>40</sup> Karyotype analysis of men with fewer than 5 million spermatozoa per milliliter of semen has been recommended as routine by the World Health Organization since 2000.<sup>41</sup> As expected, infertile men with chromosomal abnormalities are more likely to have genetically abnormal spermatozoa and to father chromosomally abnormal pregnancies.<sup>42</sup>

Azoospermia can be classified as non-obstructive or obstructive. The most common cause of obstructive azoospermia is a congenital bilateral absence of vas deferens, a feature associated strongly with mutations in the cystic fibrosis transmembrane conductance regulator genes.<sup>43,44</sup> In either presentation, a consultation with a urologist may lead to surgical extraction of sperm for use with IVF/ICSI.

Microsurgical testis sperm extraction is estimated to be successful in 50% of attempts in non-obstructive azoospermia.<sup>45</sup> Success with extracted sperm used in IVF/ICSI procedures has been documented with a pregnancy rate approaching 40%.<sup>46</sup> A recently published systematic review summarized the potential reproductive outcomes of various male reproductive genetic abnormalities associated with azoospermia. (Table 3).<sup>47</sup>

### Recommendations

1. All men with severe oligozoospermia or azoospermia (sperm count < 5 million/hpf) should be offered genetic/clinical counselling, karyotype assessment for chromosomal abnormalities, and Y-chromosome microdeletion testing prior to in vitro fertilization with intracytoplasmic sperm injection. (II-2A)
2. All men with unexplained obstructive azoospermia should be offered genetic/clinical counselling and genetic testing for cystic fibrosis prior to in vitro fertilization with intracytoplasmic sperm injection. (II-2A)

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

### Multiple Pregnancy and Adverse Obstetrical and Perinatal Outcomes

Over the last 30 years, multiple birth rates have risen dramatically internationally, associated partly with increased maternal age at pregnancy, but mostly with infertility

**Table 2. Controlled studies of obstetrical outcomes of women undergoing , compared with women conceiving spontaneously. after prolonged time to pregnancy**

Study	Adjusted for	Population	Outcome	Odds ratio
Henriksen et al. 1997 <sup>24</sup>	Parity Smoking	860 women with time to pregnancy > 12 months 6843 control subjects	Preterm birth < 37 weeks	1.7 (1.1 to 2.6) no difference with/without treatment
Draper et al. 1999 <sup>25</sup>	Potential confounders significant in logistic regression analysis	Case-controlled study of 542 women with singleton or multiple perinatal deaths 972 randomly selected control subjects Examined treated and untreated infertility in each group	Perinatal mortality	2.9 (1.8 to 4.5)
Basso and Baird 2003 <sup>26</sup>	Maternal age Pre-pregnancy BMI Smoking Social status Gender of baby	3899 (treated and untreated women with time to pregnancy > 1 year) 15 302 control subjects	GA < 37 weeks GA < 34 weeks Emergency Caesarean section	1.38 (1.14 to 1.69) 1.51 (1.05 to 2.16) 1.15 (1.00 to 1.32)
Basso and Olsen 2005 <sup>27</sup>	Maternal age BMI Smoking Social class	4142 women with TTP > 12 months 16 305 women with TTP < 12 months	Neonatal mortality within 28 days	3.32 (1.47 to 7.53) with no treatment 2.21 (0.88 to 5.55) with treatment
Thomson et al. 2005 <sup>23</sup>	Age Parity	1437 subfertile women 21 688 control subjects	Preeclampsia Placenta previa Abruption Induction of labour Caesarean section Instrumental delivery LBW	1.9 (1.5 to 2.5) 3.9 (2.2 to 7.0) 1.8 (1.1 to 3.0) 1.5 (1.3 to 1.6) 2.1 (1.8 to 2.4) 2.2 (1.8 to 2.6) 1.4 (1.3 to 1.7)
Zhu et al. 2006 <sup>28</sup>	Maternal age BMI Alcohol Smoking Occupational status	9727 pregnancies with TTP < 12 months 50 897 pregnancies with TTP < 12 months	Genital organ malformations	hazard ratio: 2.32 (1.24 to 4.35)
Zhu et al. 2007 <sup>13</sup>	Maternal age Parity Smoking	10 104 pregnancies with TTP > 12 months 51 041 pregnancies with TTP < 12 months	SGA < 5th percentile	1.24 (1.10 to 1.40) with no treatment 1.40 (1.23 to 1.60) with treatment
Romundstad et al. 2008 <sup>31</sup>	Maternal age Parity Offspring sex Year of birth Time from previous birth to conception	1 127 739 spontaneous conceptions 7474 ART conceptions 2204 women having one spontaneous conception and one ART conception (comparing outcomes in these pregnancies)	SGA (< 2 SD below mean for GA and sex) Perinatal death	1.26 (1.10 to 1.44) 1.31 (1.05 to 1.65) 0.99 (0.62 to 1.57) 0.36 (0.20 to 0.67) only significant if spontaneous conception preceded ART conception

continued

Table 2. Continued

Study	Adjusted for	Population	Outcome	Odds ratio
Jaques et al. 2010 <sup>28</sup>	No. of previous abortions	2171 singletons to subfertile women with no ART	Hypertension/PE	1.29 (1.02 to 1.61)
	Parity	4363 spontaneous pregnancy control subjects	Antepartum hemorrhage	1.41 (1.05 to 1.89)
	Private/public hospital status		Perinatal death	2.19 (1.10 to 4.36)
Raatikainen et al. 2012 <sup>30</sup>			GA < 31 weeks	1.37 (1.25 to 1.43)
			Caesarean section	1.56 (1.37 to 1.77)
	Parity	428 ART pregnancies with TTP > 2 years	Caesarean section	1.21 (0.89 to 1.64)
	Prior abortion	928 spontaneous pregnancies with TTP > 2 years	Preterm birth	1.28 (0.81 to 2.03)
	Pre-pregnancy BMI	18 984 spontaneous pregnancies with TTP < 6 months	SGA	0.95 (0.65 to 1.39)
	Scarred uterus		Need for NICU	1.28 (0.88 to 1.88)
	Smoking		Low Apgar score	1.19 (0.47 to 3.04)
Alcohol				
Maternal age				

PE: preeclampsia

treatments.<sup>48,49</sup> Multifetal pregnancy follows ovulation induction or ovarian hyperstimulation alone at rates between 5% and 40%.<sup>50</sup> The 2011 published rate of multiple pregnancies as a result of IVF reported by CARTR in Canada is approximately 30%.<sup>51</sup>

Although most multiple pregnancies following AHR are dichorionic twins, the incidence of monozygotic twins (most of whom have a monochorionic placentation) among all IVF pregnancies is estimated at 0.9% to 2%, compared with approximately 0.4% of live births from spontaneously conceived pregnancies.<sup>52–54</sup> 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%).<sup>55</sup>

Multiple pregnancy is, arguably, the most important outcome issue associated with AHR. The increased incidence of adverse outcomes for fetuses and neonates of multiple pregnancies has been consistently reported, with preterm birth and its associated sequelae the most important. The increasing overall frequency of prematurity in Canada is related to a significant degree to the increased rate of multiple pregnancy.<sup>49</sup> Much of this increase is confined to an increase in the proportion of infants born between 32 and 36 weeks' gestation, but there has also been an increase in the frequency of preterm birth before 32 weeks, from 1% to 1.2%.<sup>49</sup> In Canada, the proportion of preterm births secondary to multiple pregnancies has increased from approximately 30% in the 1970s to 58.4% in 2004.<sup>49</sup> The risks of perinatal mortality, growth restriction, cerebral palsy, and congenital anomalies are also higher in multiples than in singletons, most notably in monochorionic, but also in dichorionic, twins.<sup>49,56,57</sup>

The risk of morbidity and mortality increases with each additional fetus in a multiple gestation.<sup>58</sup> A recent two-year study at one Quebec hospital showed that 17% of all NICU admissions were from multiple pregnancies in women undergoing ART. Of these, 91% resulted from IVF, with 2 to 6 embryos transferred, and 9% from pregnancies conceived after OS.<sup>59</sup> An Australian study similarly reported that 12.3% of NICU admissions between 1994 and 2005 resulted from assisted reproduction. Of those, 5% were singletons, 27% were twins, and 65% were triplets.<sup>60</sup> There is no doubt that the increasing use of AHR has led to increased perinatal morbidity and mortality secondary to an increase in the incidence of multiple pregnancy.

Whether AHR multiples pose more risk than spontaneous multiples for perinatal adverse outcomes is less clear. Controlled studies of perinatal outcomes comparing

**Table 3. Potential reproductive outcomes of various male reproductive genetic abnormalities associated with azoospermia**

Test	Finding	Adverse consequences
Y-chromosome microdeletion	AZFc microdeletion	Male offspring with severe spermatogenetic failure/sterility
	AZFc microdeletions with aberrations in pseudoautosomal regions (PARs)	Male offspring with severe spermatogenetic failure/sterility; possible skeletal or other anomalies
	gr/gr microdeletion	Male offspring with severe spermatogenetic failure/sterility; possible skeletal or other anomalies
Karyotype analysis	47, XXY (Klinefelter syndrome)	Hypogonadism, slightly increased rate of autosomal and sex chromosomal disomy in sperm; offspring with 46XX or 46XY karyotype with no genetic anomalies
	Isodicentric Y chromosome	Possible offspring with 45X, Turner's syndrome, or mixed gonadal dysgenesis (45,X/46,XY)
	Chromosome translocations	Depends on chromosomes involved; recurrent pregnancy loss or aneuploidy of offspring
CF mutation analysis	Congenital bilateral absence of vas deferens	Offspring with possible mild cystic fibrosis disease spectrum if partner is a carrier; renal abnormalities if no CFTR mutation identified
Sperm morphology	Structural aberrations of the spermatozoon (e.g. Globozoospermia, dysplasia of the fibrous sheath)	No obvious congenital anomalies in offspring reported but possible higher rates of embryo aneuploidy

CFTR: Cystic fibrosis transmembrane conductance regulator

Adapted from Hamisch and Oates, 2012.<sup>47</sup>

twin pregnancies conceived after AHR with those of spontaneously conceived twins,<sup>61-67</sup> as well as 2 systematic reviews,<sup>68,69</sup> reveal data that are somewhat conflicting. The study quality is hampered by several factors, including small sample size, retrospective design, and inability to accurately identify pregnancies conceived by ART (IVF or IVE/ICSI) versus other forms of AHR (OI, OH, or OI/OH-IUI), with some studies likely incorrectly classifying the latter in the “spontaneous” group. As well, the known effects of chorionicity and subfertility themselves are inconsistently controlled. Finally, the fact that women undergoing AHR treatments generally attend prenatal care earlier, and are followed more closely, could confound the results.

With these limitations in mind, recent studies have suggested very little independent influence of ART on adverse outcome between these 2 comparison groups, with some showing better outcomes within the ART group. Joy et al. found an increase in preterm birth, lower birth weight, and congenital anomalies among the spontaneously conceived twins, but these findings were negated when the monozygotic twins were removed.<sup>70</sup> Morcel et al. found that differences in outcomes were related to chorionicity and method of AHR, with higher risk among pregnancies conceived by OI than by ART,<sup>66</sup> and Verstraelen et al. suggest that subfertility itself plays a significant role in adverse outcomes.<sup>64</sup>

Maternal complications are more common in multiple pregnancies than in singletons. Anemia, gestational hypertension,<sup>71</sup> preeclampsia, gestational diabetes, operative

risks from Caesarean section, and postpartum hemorrhage are of increased concern with multiple pregnancy.<sup>72</sup>

As well as medical complications, multiple births generate significant economic and psychosocial costs.<sup>73-75</sup> Interestingly, a recent study found, among parents of both ART and spontaneous pregnancies, that the mental health of both parents was more adversely affected by multiples than by singletons, but that ART did not have an additional adverse effect.<sup>76</sup>

Multifetal reduction can be very emotionally difficult for couples who have gone through fertility treatment, particularly when the procedure may result in the loss of the entire pregnancy.<sup>77</sup> Although some studies document a risk of long-term adverse emotional consequences for the couple,<sup>78-80</sup> current evidence supports multifetal pregnancy reduction of higher order multiples to twins in order to improve pregnancy outcomes.<sup>81,82</sup> Compared with spontaneously conceived twin pregnancies, twin pregnancies remaining after fetal reduction continue to have an increased risk of preterm birth, LBW, very low birth weight, and fetal growth restriction.<sup>62,83</sup>

Because of these maternal and perinatal risks, there has been significant international effort to reduce the incidence of multiple pregnancy associated with AHR. Transfer of fewer embryos per cycle will reduce multiple pregnancy rates, but this beneficial effect may be accompanied by a less than acceptable pregnancy rate.

Two recent systematic reviews examined this topic. A 2009 Cochrane review compared the live birth rate of elective DET with that of elective single, triple, or quadruple embryo transfer. The review concluded that a single cycle of eSET resulted in a lower live birth rate than DET, but that the *cumulative* live birth rate in a fresh eSET cycle followed by a frozen eSET was not significantly different from a single DET cycle.<sup>84</sup>

A second meta-analysis by Grady et al. in 2012 compared perinatal outcomes between DET and eSET pregnancies. They found an RCT-based relative risk of 0.37 (0.25 to 0.55) for preterm birth < 37 weeks, and a RCT-based RR of 0.25 (0.15 to 0.45) for birth weight < 2500 g in the eSET group.<sup>85</sup> Upon consideration of these results, it appears likely that with a policy of fresh eSET followed, as necessary, by a cycle of frozen eSET, the cumulative live birth rate would be very similar to DET.

Many clinicians differentiate between live birth rates and perinatal outcomes with IVF in women under and over 40 years of age, but these 2 studies did not. A recent observational UK study of 33 514 live births in 124 148 IVF cycles examined these outcomes according to whether 1, 2, or  $\geq 3$  embryos were transferred in women aged < 40 or  $\geq 40$ . The study found that the overall live birth rate was better in the < 40 age group, that the live birth rate was higher for DET than for SET in both age groups, that perinatal outcomes were worse in both age groups for DET than for SET, but, notably, that the difference in adverse perinatal outcomes in DET versus SET was less in the > 40 age group. This large observational study supports consideration of DET for women  $\geq 40$ . The study showed that transferring more than 2 embryos did not increase live birth rates in either age group, and it discouraged transferring 3 or more embryos at any stage.<sup>86</sup>

The potential impact of a policy of eSET in appropriately selected women on perinatal and maternal outcomes is significant, and such a policy could result in substantial cost savings. One modelling study examined the cost utility of this policy,<sup>87</sup> and a multi-centre cohort examining the long-term effects and cost implications of the Dutch policy of eSET is ongoing.<sup>88</sup>

Based on this research, ESHRE,<sup>89</sup> HFEA,<sup>90</sup> ASRM,<sup>91</sup> and SOGC and CFAS (jointly)<sup>92</sup> have modified their guidelines and recently endorsed a policy of eSET for women with clinical factors predictive of a high chance of success for cumulative live birth in centres with a good cryopreservation facility. However, there is no current specific predictive model to facilitate broad policy recommendations in

terms of number of embryos transferred, and the current recommendations<sup>93</sup> suggest that individual IVF-ET programs should evaluate their own data to identify patient-specific, embryo-specific, and cycle-specific determinants of implantation and live birth in deciding on the number of embryos to transfer. Updated recommendations will likely consider the age of the woman or the egg donor to be paramount in this decision-making process.

Internationally, in some jurisdictions the proportion of eSET has increased and the multiple birth rate has fallen. The 2010 US data report an approximate 15% eSET rate<sup>94</sup> (twice that of 2000), while 2011 data from the UK report a 16.8% eSET rate.<sup>95</sup> The 2011 UK data show a significantly lower (20.6%) multiple pregnancy rate<sup>95</sup> than the 2010 US rate of 31%.<sup>94</sup>

Recently, AHRC analyzed the current international and national state of AHR policy on embryo transfer. An overriding factor that surfaced as a barrier to a broader practice of eSET was active government legislation, often linked to reimbursement. Those jurisdictions with legislation and funded programs had much higher rates of eSET; Belgium, Finland, and Australia approach 50% eSET rates, with funded programs and linked legislation promoting maximal use of eSET.

In Canada, an expert panel in Ontario has recommended consideration of legislation and public funding for higher rates of eSET.<sup>96</sup> As of August 5, 2010, the provincial government of Quebec began funding 3 cycles of IVF with OS or up to 6 cycles of natural or modified natural cycles of IVF, with IVF funding tied to eSET for clinically favourable situations. An initial report on the first 3 months of the program in 2009 found an increase in the rate of eSET from 1.6% to 50%, and a reduction in the multiple pregnancy rate from 25.6% to 3.7%.<sup>97</sup> The most recent report indicates an eSET rate of 49%, a 5.2% multiple pregnancy rate, and a predicted cumulative pregnancy rate of 60% per cycle.<sup>98</sup>

Although most of the attention in reducing multiple pregnancy rates has been directed at strategies related to IVF, studies are increasingly addressing strategies related to OI and OH with gonadotropin medications. This latter literature is complicated by heterogeneity in both the patient population and the medication regimens aimed at OI or OH, with or without IUI. In addition, unlike ART/IVF, there is even less regulation and capture of data on treatment outcomes in this population, as it is not subject to either mandatory or voluntary AHR reporting in North America or Europe.



A recent review<sup>99</sup> and ASRM committee opinion on ways to reduce multiple pregnancy rates following OI/OS reviews several strategies that have been studied, including longer initial treatment with clomiphene citrate prior to gonadotropin use, lower doses of gonadotropins, and monitoring and altering cycle management on the basis of estradiol levels and follicle size. The committee concludes that useful work has been done, but larger, prospective studies are needed prior to the issue of a formal guideline on this issue.<sup>100</sup>

### Recommendations

3. Multiple pregnancy is the most powerful predictive factor for adverse maternal, obstetrical, and perinatal outcomes. Couples should be thoroughly counselled about the significant risks of multiple pregnancies associated with all assisted human reproductive treatments. (II-2A)
4. The benefits and cumulative pregnancy rates of elective single embryo transfer support a policy of using this protocol in couples with good prognosis for success, and elective single embryo transfer should be strongly encouraged in this population. (II-2A)
5. To reduce the incidence of multiple pregnancy, health care policies that support public funding for assisted human reproduction, with regulations promoting best practice regarding elective single embryo transfer, should be strongly encouraged. (II-2A)

### Singleton Pregnancies and Perinatal Outcome

AHR resulting in singleton pregnancies has also been shown to be associated with adverse obstetrical and perinatal outcomes, but this is challenging literature to analyze. There are many individual factors that can independently and significantly contribute to adverse outcomes, but they are difficult to isolate as they are interrelated with the couple's clinical profile (reason for infertility/subfertility) and treatment regime.

The quality of studies has improved as accumulated data from large registries have been published, but these still do not allow the isolation of likely important but interrelated clinical details, such as maternal and paternal background factors and individual factors within the treatment regimes. Different forms of OI versus OH, donor versus own eggs, timing and/or method of aspiration of eggs, maturation in an artificially high hormonal milieu in the mother (OH) or in the laboratory (in vitro maturation), fresh or frozen embryos, method of freezing embryos or eggs, origin of sperm (ejaculated, testicular, epididymal), quality of sperm, number of embryos formed, number of embryos transferred, stage of transfer (cleavage vs. blastocyst

stage), and the effect of “vanishing” fetuses are some of the factors that could affect perinatal, obstetrical, and long-term outcomes in different but significant ways.

There are, however, some evolving trends that continue to support the association between AHR and increased risk of adverse obstetrical and perinatal outcomes among singleton pregnancies.

### Preterm Birth

Along with multiple pregnancy, preterm birth and LBW are the most commonly examined measures of adverse perinatal outcome in singleton pregnancies conceived after AHR.<sup>101,102</sup> Table 4 summarizes these data.<sup>96–99,101,103</sup>

Several studies have found an increased risk of preterm birth, whether defined as birth before 37 weeks, at 32 to 36 weeks, or before 32 weeks, in IVF versus spontaneous singleton pregnancies. Adjusted odds ratios/relative risks are between 1.95 and 3.22.<sup>104–108</sup> It is not as convincing that OI alone increases the risk of preterm birth once other factors are controlled,<sup>109,110</sup> although one recent large Finnish cohort study found an independent effect on preterm birth in all categories of gestational age cut-offs.<sup>111</sup>

### Low Birth Weight

In almost all studies of singleton pregnancies resulting from any type of AHR, LBW is found more often than in spontaneous pregnancies. As in preterm birth, all systematic reviews have associated IVF with reduced birth weight, as indicated in Table 4.<sup>69,82,105–108</sup> LBW in these cases reflects not only decreased gestational age, but also less than optimal growth for a given gestational age.

OI is also quite consistently associated with LBW.<sup>109–111</sup> Exposure to gonadotropic stimulation, which produces increased physiologic levels of circulating estradiol combined with in vitro culture may be cumulatively detrimental to normal embryo growth.<sup>112</sup>

Many emerging studies are attempting to isolate the causative factors responsible for growth disturbance in women undergoing AHR by comparing outcomes in various subsets within cohort studies of the AHR population and with outcomes in spontaneous pregnancies. Consistent with the data on the contribution of the diagnosis and causes of infertility itself, Sasanova et al. performed logistic regression analysis on 8941 singleton pregnancies after IVF to determine predictive factors for preterm birth and LBW. They found that primiparity, smoking, BMI, and the vanishing twin phenomenon increased the risk of preterm birth, and that maternal age, smoking, BMI, and duration of infertility increased the risk of LBW.<sup>113</sup>

**Table 4. Controlled studies of preterm birth and LBW among singleton pregnancies after AHR, compared with spontaneously conceived pregnancies**

Perinatal outcomes	RR IVF (95% CI)	RR ovulation induction alone (95% CI)
Preterm delivery < 37 weeks	1.98 (1.77 to 2.22) <sup>97</sup>	1.32 (1.15 to 1.50) <sup>104</sup>
	2.00 (1.70 to 2.20) <sup>98</sup>	
	1.93 (1.36 to 2.74) <sup>99</sup>	
	1.84 (1.54 to 2.21) <sup>100</sup>	
	1.91 (1.31 to 2.80) <sup>101</sup>	
Preterm delivery 32–36 weeks or < 32 weeks	2.3 (1.00 to 5.28) <sup>99</sup>	1.52 (1.13 to 2.04) <sup>104</sup>
Low birth weight < 2500 g	1.40 (1.01 to 1.95) <sup>99</sup>	1.43 (1.23 to 1.67) <sup>104</sup>
	2.20 (1.55 to 3.13) <sup>103</sup>	
	1.40 (1.01 to 1.95) <sup>100</sup>	
Very low birth weight < 1500 g	3.78 (2.49 to 5.75) <sup>99</sup>	3.1 (1.0 to 10.4) <sup>102</sup>
	2.7 (1.8 to 4.1) <sup>102</sup>	
SGA < 10th percentile	1.98 (1.21 to 3.24) <sup>103</sup>	1.71 (1.09 to 2.69) <sup>103</sup>

A number of studies that compared IVF cycles with fresh versus frozen (cryopreserved) embryos found that frozen embryo transfers result in higher birth weights, a lower chance of SGA infants, and a lower rate of preterm birth.<sup>114–116</sup> A large Australian cohort study performing regression analysis to determine predictive factors for LBW reports a significant increase in LBW with fresh versus FET, with an aOR of 1.9 (95% CI 1.6 to 2.4).<sup>117</sup>

A systematic review on the topic also reports that the preterm birth rate is either unchanged or decreased, and the LBW/SGA rate is unchanged or improved with cryopreserved versus fresh IVF cycles.<sup>118</sup> A recent American cohort study of 24 334 singleton fresh IVF pregnancies compared with 13 806 singleton FET IVF pregnancies found no significant increase in aORs for preterm birth with FET, but an increase in the overall rate of LBW, with an aOR of 1.35 (95% CI 1.20 to 1.51) among pregnancies of fresh IVF cycles. In donor oocyte cycles with no OS, the rate of LBW was not increased.<sup>119</sup> These findings suggest that changes in the uterine environment associated with multiple follicle production increases the risk of LBW.

An interesting Danish cohort study of sibling singleton births comparing 5 groups of successive pregnancies

- fresh IVF-ICSI vs. spontaneous,
- fresh IVF-ICSI vs. FET,
- FET vs. FET,
- fresh IVF-ICSI vs. fresh IVF-ICSI,
- spontaneous vs. spontaneous

found a higher risk of LBW and lower mean birth weight in fresh IVF-ICSI pregnancies than in FET, and an overall lower birth weight with any ART than with spontaneous pregnancy.<sup>120</sup>

The most recent data from a cohort of 25 777 births documents a significant difference in birth weight of 90.9 g in singletons conceived in frozen versus fresh transfer cycles.<sup>121</sup>

There is speculation that the endometrial environment may be improved by the lower doses of OS agents required for FET, or that better quality embryos are recruited and persevere through cryopreservation procedures. However, another cohort study of 32 416 singleton IVF or ICSI pregnancies found no independent relationship between the parameters of OS used in these cycles and birth weight.<sup>122</sup>

An interesting study of 292 singletons examined serum estradiol levels during IVF cycles found that adjusted for patient age, BMI, parity, number of embryos transferred, day of transfer, and gonadotropin dose, high serum estradiol levels (> 3450 pg/mL or > 90th percentile) were associated with preeclampsia (OR 4.8; 95% CI 1.6 to 14.8) and SGA (OR 9.4; 95% CI 3.2 to 27.5).<sup>123</sup>

Other studies have compared pregnancies conceived after ICSI/IVF to spontaneous pregnancies with regard to preterm birth and LBW. Two small studies (N = 41 ICSI/147 control subjects<sup>124</sup>; N = 276 ICSI/273 control subjects<sup>125</sup>) comparing IVF/ICSI pregnancies with

spontaneous pregnancies did not find an increase in LBW or preterm birth. A study comparing 81 singleton ICSI pregnancies to 81 matched-control IVF pregnancies did not find any significant difference in preterm birth or low birth weight.<sup>126</sup> A Canadian study comparing ICSI ( $n = 104$ ), IVF ( $n = 133$ ) and in vitro ovum maturation ( $n = 31$ ) did not find any significant differences in rates of preterm birth or LBW.<sup>127</sup> The source of sperm for ICSI (ejaculated, epididymal, or testicular) does not appear to influence birth weight parameters.<sup>128,129</sup> ICSI itself does not appear to adversely affect preterm birth or LBW rates.

Use of donor, versus autologous, oocytes has been reported to increase the risk of preterm birth and LBW. A small case-controlled study comparing 81 IVF donor cycles to 77 autologous oocyte IVF cycles found an increased aOR of 2.6 (95% CI 1.04 to 6.3) for preterm birth.<sup>130</sup> A SART report comparing 60 037 standard IVF cycles with 10 176 donor egg cycles and 1180 gestational carrier cycles found aORs of 1.21 (95% CI 1.13 to 1.30) for birth weight < 2500 g and 1.28 (95% CI 1.10 to 1.49) for birth weight < 1500 g when comparing donor egg with autologous egg IVF cycles.<sup>37</sup>

### Other Obstetrical Outcomes

There has been some question of whether AHR leads to placental abnormalities as a mediating factor for some adverse outcomes, such as LBW, preeclampsia, abnormal implantation, placenta accreta, antepartum hemorrhage, and postpartum hemorrhage. Possible early placental abnormalities are consistent with the finding of altered levels of maternal serum marker levels for Down syndrome and open neural tube defects in the first and second trimester. Several studies, including that reported from the Danish cohort, found a significantly lower PAPP-A level among ART pregnancies (except those with FET) of 0.8 MoM<sup>131</sup> and an elevated total hCG.<sup>132</sup>

Several studies report an increased risk of preeclampsia with AHR. Calhoun reports an aOR of 2.2 (95% CI 1.03 to 4.72), when controlling for factors including multiple gestation, for preeclampsia with AHR; the risk was greatest for IVF (aOR 5.3; 95% CI 1.74 to 15.89), and there was no reported association between IUI and preeclampsia.<sup>133</sup>

Two separate cohort studies from the same Ontario database report somewhat contradictory findings. Sun et al. found a non-significant increased risk of a composite outcome of placenta-mediated complications (stillbirth, growth restriction, preeclampsia, and abruption) with IUI (OR 1.30; 95% CI 0.94 to 1.80) but not with IVF or OI in a matched-control study in singletons.<sup>134</sup> Another analysis on

an overlapping cohort from the same database controlling for, but not excluding, multiples, reports an increased risk for preeclampsia with IVF (OR 1.78; 95% CI 1.05 to 3.06), but not for IUI or OI.<sup>135</sup> Small studies have linked donor oocytes with an increased risk of preeclampsia over autologous oocytes.<sup>130,136</sup>

Other placental complications reported to occur with increased frequency with ART include placenta previa, placental abruption, and antepartum and postpartum hemorrhage. In a review of 42 placenta accreta cases, the OR for IVF versus spontaneous pregnancies was 13.2 (95% CI 6.7 to 25.8).<sup>137</sup> A large Australian cohort study of 6730 IVF/ICSI pregnancies compared with 24 619 spontaneous pregnancies found an aOR of 2.0 (95% CI 1.8 to 2.3) for antepartum hemorrhage, 2.3 (95% CI 1.9 to 2.9) for placenta previa, 2.1 (95% CI 1.4 to 3.0) for abruption, and 1.3 (95% CI 1.2 to 1.4) for postpartum hemorrhage.<sup>138</sup> A recent systematic review of 13 studies did not indicate an increased risk of postpartum depression associated with ART.<sup>139</sup>

The timing of the transfer of the embryo in IVF or IVF/ICSI may influence the outcome. Optimal timing has evolved from the cleavage-stage to the blastocyst stage, as the success rate after blastocyst transfer is higher, resulting in a higher live birth rate.<sup>140</sup> In a meta-analysis of 4 studies of 1102 blastocyst transfer cycles versus 1485 cleavage-stage cycles, the ratio of males to females was higher (OR 1.29; 95% CI 1.10 to 1.51) in blastocyst transfer cycles. In the same report a meta-analysis of 7 studies of 9316 blastocyst cycles versus 31 601 cleavage-stage cycles found the rate of monozygotic twinning to be increased with blastocyst transfer (OR 3.04; 95% CI 1.54 to 6.01).<sup>141</sup> In another study of 1311 blastocyst transfer cycles versus 12 562 cleavage-stage cycles, the rate of birth < 37 weeks was slightly increased in the blastocyst transfer group (OR 1.35; 95% CI 1.07 to 1.71), but the LBW rate was unchanged.<sup>142</sup>

### Long-Term Child Outcomes

Several large registry-based studies examining long-term child outcomes have been published recently. There appears to be little, if any, increased risk of significant neurodevelopmental or behavioural adverse outcomes at 2-year<sup>124</sup> or 5-year<sup>125,143</sup> follow-ups. A 10-year follow-up study found no significant difference between ICSI and spontaneously conceived children.<sup>144</sup> Physical health, thus far, appears equal, although there has been a reported increase in undescended testes and resulting urogenital surgery in boys after ICSI.<sup>145</sup> Although small studies reported an increase in certain childhood cancers, registry data do not support this relationship.<sup>146</sup>

## Recommendations

6. Among singleton pregnancies, assisted reproductive technology is associated with increased risks of preterm birth and low birth weight infants, and ovulation induction is associated with an increased risk of low birth weight infants. Until sufficient research has clarified the independent roles of infertility and treatment for infertility, couples should be counselled about the risks associated with treatment. (II-2B) There is a role for closer obstetric surveillance for women who conceive with assisted human reproduction. (III-L)
7. There is growing evidence that pregnancy outcomes are better for cryopreserved embryos fertilized in vitro than for fresh embryo transfers. This finding supports a policy of elective single embryo transfer for women with a good prognosis (with subsequent use of cryopreserved embryos as necessary), and may reassure women who are considering in vitro fertilization. (II-2A)
8. Women and couples considering assisted human reproduction and concerned about perinatal outcomes in singleton pregnancies should be advised that (1) intracytoplasmic sperm injection does not appear to confer increased adverse perinatal or maternal risk over standard in vitro fertilization, and (2) the use of donor oocytes increases successful pregnancy rates in selected women, but even when accounting for maternal age, can increase the risk of low birth weight and preeclampsia. (II-2B)

## FETAL STRUCTURAL, CHROMOSOMAL, AND IMPRINTING ABNORMALITIES ASSOCIATED WITH ASSISTED HUMAN REPRODUCTION

### Structural Abnormalities (Malformations, Deformations, and Disruptions)

Previous studies of the association between ART and structural congenital malformations have reported an elevated risk, but were limited by small sample sizes, varying definitions of congenital anomalies, and lack of data on potential confounding variables.<sup>147-149</sup> A longitudinal study of the Danish national birth cohort found that singletons born to couples with a history of infertility, but who conceived naturally *or* with ART treatment had a higher prevalence of congenital malformations (HR 1.20; 95% CI 1.07 to 1.35) than babies born spontaneously with no delay in time to conception. Babies born of ART in infertile couples had an increased prevalence of genital organ malformations (HR 2.32; 95% CI 1.24 to 4.35).<sup>27</sup>

The National Birth Defects Prevention Study provided a case-controlled analysis of registered live-born infants versus those born through ART for congenital defects. Adjustments for confounders included maternal race, maternal age, smoking, and parity. ART was associated with septal heart defects (aOR 2.1; 95% CI 1.1 to 4.0); esophageal atresia (aOR 4.5; 95% CI 1.9 to 10.5), and anorectal atresia (aOR 3.7; 95% CI 1.5 to 9.1). Among multiple births, there was no significant association between ART and birth defects.<sup>150</sup>

The findings of a recent retrospective cohort study of IVF/ICSI patients in a Canadian centre suggest there is a higher prevalence of infants with congenital heart defects in infants conceived by IVF/ICSI (1.1%) than in spontaneously conceived infants (0.4%) ( $P < 0.01$ ). A maternal BMI of  $> 30 \text{ kg/m}^2$  was found to increase this prevalence of birth defects.<sup>151</sup>

More recent registry data demonstrate a higher risk for major congenital abnormalities in infants following both IVF and IVF-ICSI than in spontaneous conceptions, after adjusting for appropriate confounding factors.<sup>152</sup> 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%), and a 2-fold risk for major malformations in one or both newborns among twin gestations following IVF-ICSI, compared with singletons following IVF-ICSI.<sup>149,153</sup> A meta-analysis reviewing data from 46 different studies, including 124 468 infants conceived with ART, compared with spontaneously conceived children, showed that the total adjusted RR for ART procedures versus spontaneous conception was 1.36 (95% CI 1.26 to 1.48), with no difference seen between IVF and IVF/ICSI.<sup>154</sup>

Davies et al.<sup>38</sup> compared the incidence of birth defects, including births and terminations of pregnancy, in patients in South Australia undergoing IVF (with or without ICSI) with those of spontaneous pregnancies. Among the total IVF cases ( $\pm$  ICSI), the aOR for IVF  $\pm$  ICSI was 1.28 (95% CI 1.16 to 1.41). Comparing IVF alone to spontaneous pregnancies resulted in the loss of any significant effect of ART, while IVF/ICSI remained a significant risk factor, with an aOR of 1.57 (95% CI 1.30 to 1.90). In the same population ( $N = 308\ 974$ ), the incidence of birth defects with a history of infertility, with or without ART, was higher than among spontaneous pregnancies without a history of infertility.<sup>2</sup>

## Recommendations

9. Any assisted reproductive technology procedure should be prefaced by a discussion of fetal outcomes and the slight increase in the risk of congenital structural abnormalities, with emphasis

**Table 5. Human phenotypes identified and associated with imprinted genes**

Syndrome	Chromosome location
1. Beckwith-Wiedemann	11p15
2. Angelman	15q11-q12 maternal
3. Prader-Willi	15q11-q12 paternal
4. Silver-Russell	7p11-p13, 7q31-qter, 11p15
5. Transient neonatal diabetes mellitus	6q24
6. McCune Albright	20q13
7. Familial nonchromaffin paraganglioma	11q13
8. Maternal and paternal uniparental disomy	2, 14, 16
9. Turner	X

on known confounding factors such as infertility and body mass index. (II-2B)

10. In pregnancies achieved by assisted reproductive technology, routine anatomic ultrasound for congenital structural abnormalities is recommended between 18 and 22 weeks. (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 those in spontaneously conceived pregnancies (0.2%), but significantly higher following IVF-ICSI (1.0%).<sup>149</sup> Significantly more de novo chromosomal aberrations have been diagnosed prenatally in children conceived by IVF-ICSI than the general newborn population.<sup>155</sup> A prospective clinical observation study<sup>156</sup> analyzed peripheral and umbilical cord blood samples of male children born to fathers with normal spermatogenesis. De novo Y-chromosome microdeletions were identified in 5.3% of 19 IVF offspring and in 16.7% of 18 ICSI offspring; both techniques were statistically significantly associated with a higher rate of de novo Y-chromosome microdeletions than in male children conceived naturally.

As in spontaneously conceived pregnancies, options for prenatal diagnosis of aneuploidy (chorionic villus sampling or amniocentesis) in patients who conceive after AHR should be determined by results of prenatal screening tests for aneuploidy,<sup>156</sup> except for those resulting from IVF-ICSI.<sup>154</sup>

Most studies find no significant differences between nuchal translucency measurements in IVF and IVF-ICSI pregnancies and in spontaneously conceived pregnancies.<sup>158</sup> PAPP-A levels have been found to be significantly lower after ART.<sup>159</sup> MSAFP is not a reliable marker for neural tube defects following fetal reduction.<sup>160</sup> Elevated MSAFP levels have been observed in pregnancies conceived with donor oocytes.<sup>161</sup>

### Recommendation

11. Pregnancies conceived by intracytoplasmic sperm injection may be at increased risk of chromosomal aberrations, including sex chromosome abnormalities. Diagnostic testing should be offered after appropriate counselling. (II-2A)

### Imprinting Disorders

Pregnancies using ART are increasing with the availability of the technology and with patient needs and choices, and recent estimates indicate that in industrialized and developed countries 1.7% to 4.0% of all children are born after ART.<sup>2</sup> The first live-born offspring after IVF, FET, and ICSI were reported in 1978, 1984, and 1992.<sup>162–164</sup>

The association between adverse pregnancy outcomes and genetic imprinting errors with the identification of epimutations is rare, but understanding of the mechanisms through animal and human research is quickly expanding.

Genomic imprinting is a process of epigenetic modification which allows genes to be expressed in a parent-of-origin-specific manner. These genetic loci are important for normal growth and development. Imprinting is found predominately in placental mammals and may have evolved as a mechanism to balance the allocation of parental resources to the offspring.<sup>164,6</sup> Epigenetics is the modification of the “complete” DNA structure by methylation or histones that results in the gene becoming non-transcribed in a time-specific period or a tissue-specific fashion, but with no alteration of the actual DNA coding sequence in the gene. Nine human phenotypes have been identified and associated with an imprinted gene (Table 5).<sup>165,166</sup>

The imprinting loci/epimutations in phenotypes that have been strongly associated with children conceived with ART are Beckwith-Wiedemann syndrome, Silver-

Russell syndrome, and Angelman syndrome. The reported evidence of association between these imprinting phenotypes and various ART techniques, including IVF and ICSI, have been confined to epimutations.

There are a number of potential mechanisms by which ART could contribute to the creation of epimutations. The composition/culture of the media environment, disruption of maternally-imprinted genes with super-ovulation, hypomethylation of paternal or maternal genes, or, as with the other potential adverse outcomes perhaps incorrectly associated with ART, the underlying condition responsible for infertility, could all be associated with imprinting abnormalities.<sup>17</sup>

While the association between imprinting and ART has biological plausibility and strong data from animal and human species, the overall risk for a child to be born with an imprinting defect following ART is low. The probable increased imprinting-associated ART risks are related to the phenotypes Silver-Russell syndrome and Beckwith-Wiedemann syndrome, with less evidence supporting the association with Angelman syndrome and Prader-Willi syndrome.

Studies have proposed that ART children are at a greater risk of later malignancy, with a possible etiology of reduced imprinted gene activity leading to dysregulation in tumour suppression.<sup>168</sup> Large follow-up studies suggest an increased cancer risk in ART children, but other confounding factors, such as prematurity and asphyxia, may be in play.<sup>169</sup> Further studies are required, as the majority of the ART cohort is under age 30.<sup>169</sup>

A 2009 review concluded that “epigenetic aberrations can result in outcomes as specific as Beckwith-Wiedemann syndrome or as diffuse as growth restriction.”<sup>167</sup> Substantial evidence exists from animal and human studies that gametogenesis and preimplantation are vulnerable to epimutations. Whether ART introduces epigenetic aberrations during these critical times, or whether epimutations are more frequent in individuals with infertility, remains unresolved.<sup>167</sup>

### Summary Statement

2. The relative risk for an imprinting phenotype such as Silver-Russell syndrome, Beckwith-Wiedemann syndrome, or Angelman syndrome is increased in the assisted reproduction population, but the actual risk for one of these phenotypes to occur in an assisted pregnancy is estimated to be low, at less than 1 in 5000. The exact biological etiology for this imprinting risk increase is likely heterogeneous and requires more research. (II-2)

### Recommendation

12. The possible increased risk for late onset cancer due to gene dysregulation for tumour suppression requires more long-term follow-up before the true risk can be determined. (III-A)

### Preimplantation Genetic Screening

Recently, more ART cycles have incorporated preimplantation genetic screening for aneuploidy or random genetic error at the stage of the embryo to increase the chance of a successful live birth. The process includes the microscopic biopsy of embryos at 72 hours of age to isolate a blastomere or trophoctoderm tissue at the blastocyst stage of development. Genomic analysis is then done using traditional fluorescent in situ hybridization analysis of 5 to 7 chromosomes or, more recently, whole genome analysis using comparative genomic hybridization.<sup>170,171</sup> Indications for the application include advanced maternal age, repeated IVF failure, recurrent miscarriage, and testicular sperm extraction.

The literature remains controversial with respect to the testing's proven benefit in terms of a healthy live birth as an outcome and, more specifically, with respect to the well-being of that infant. A recent report of a series of 581 children born after PGS found that birth weight and major malformation rates were not statistically different from those of other IVF/ICSI children.<sup>172</sup> The same study also reported the misdiagnosis rate was less than 1%. A further prospective blinded follow-up study of children born to women randomly assigned to receive PGS or not found that the technique was not associated with impaired mental, psychomotor, or behavioural outcomes by age 2 years, although there was a suggestion that with detailed neurological testing, PGS was associated with a less “optimal” neurological testing score.<sup>173</sup> More recently the same group reported on the follow-up of the same cohort at 4 years of age. They found no effect of PGS on singletons in the cohort, but a significant negative difference in neurological testing scores among twins after PGS.<sup>174</sup> Thus the effects of preimplantation genetic screening on long-term outcomes are unclear.

A recently published technical update has reviewed preimplantation screening and diagnosis in more detail.<sup>175</sup>

### Recommendations

13. The clinical application of preimplantation genetic testing in fertile couples must balance the benefits of avoiding disease transmission with the medical risks and financial burden of in vitro fertilization. (III-B)

14. Preimplantation screening for aneuploidy is associated with inconsistent findings for improving pregnancy outcomes. Any discussion of preimplantation genetic screening with patients should clarify that there is no adequate information on the long-term effect of embryo single cell biopsy. (I-C)

**SUMMARY**

As with knowledge of outcomes in other emerging and developing technologies, there continue to be gaps in our knowledge of the association of AHR with maternal, perinatal, and childhood outcomes. A recent discussion paper prepared for AHRC on reproductive outcomes after AHR has emphasized the importance of comprehensive outcomes surveillance systems that build on the current CARTR database, with personalized health information, measurable outcomes including long-term and developmental outcomes, and the ability to link to other relevant national and international databases.<sup>1</sup>

There has been an improvement in the quality of data with the accumulation and accuracy of large population databases and improved linkage of AHR parameters to birth and early childhood outcomes, but ongoing efforts in this area are critical to further specify the differential association of underlying infertility factors and details of AHR on outcomes.

The majority of pregnancies resulting from AHR are uncomplicated and result in the birth of healthy children. However, it is also clear that when TTP are greater than one year, a higher proportion of AHR pregnancies than spontaneous pregnancies are associated with obstetrical and perinatal complications, whether it be a result primarily of underlying parental factors leading to infertility or of specific AHR techniques.

The majority of obstetric and pediatric problems after AHR arise as a result of multiple pregnancies. Much new evidence has accumulated to encourage the use of eSET where appropriate and, when applied, this has been shown to markedly reduce the multiple pregnancy rate. Counselling of prospective parents should incorporate this knowledge.

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