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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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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 Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice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
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	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.[176]

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

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

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)
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)
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 of 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 risks of low birth weight and preeclampsia. (II-2B)
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 on known confounding factors such as infertility and body mass index. (II-2B)
10. In pregnancies achieved by artificial reproductive technology, routine anatomic ultrasound for congenital structural abnormalities is recommended between 18 and 22 weeks. (II-2A)
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)
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)
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)