

OHTAC Recommendation

In Vitro Fertilization and Multiple Pregnancies

October 19, 2006

OHTAC Ontario
Health Technology
Advisory Committee

In Vitro Fertilization and Multiple Pregnancies

The Ontario Health Technology Advisory Committee (OHTAC) met on October 19, 2006 and reviewed the health technology assessment report on the current role of IVF in management of infertility and the potential for expanding IVF coverage. The review included a presentation by the Medical Advisory Secretariat (MAS) and discussion.

Infertility affects about 8.5-15% of reproductive age couples. It could be caused by a number of factors including: sperm abnormalities, ovulatory failure, tubal obstruction due to infection or damage, and unexplained (idiopathic) infertility. The cause of infertility dictates the choice of therapeutic options. These options from the least invasive to the most invasive treatment are: pharmacological stimulation of ovaries, intra-uterine insemination (IUI), in-vitro fertilization (IVF), and IVF with intra-cytoplasmic sperm injection (ICSI).

In IVF, the most technologically advanced treatment today, eggs (ova) are retrieved from the ovaries, exposed to sperm outside the body and fertilized. The resulting embryo(s) is cultured for 3 to 5 days, and transferred back to the uterus. When ICSI is added to IVF, fertilization occurs through microinjection of a single sperm into the ovum.

Currently, in Ontario OHIP covers 3 cycles of IVF only in cases of bilateral tubal obstruction, which comprises less than a third of all patients undergoing IVF treatment. For these patients, this is the only way in which fertilization can occur. Most of the IVF procedures in the province are done in private clinics. There are 13 clinics in Ontario offering IVF, and about 4,300 cycles of IVF are performed annually. The average rate of live births after IVF is 31%, but it varies considerably by the woman's age, being highest in women under 35 years (38%) and decreasing rapidly beyond this age.

One of the potential consequences of infertility treatment is multiple pregnancy, which is associated with a number of maternal and neonatal complications. Unlike other treatment options, IVF allows direct control over the number of embryos transferred in each treatment cycle and thus may help to eliminate or significantly reduce the risk of multiple pregnancy associated with infertility treatment. This served as the rationale for the Infertility Awareness Association of Canada (IAAC) to advocate the broader use of IVF and to request expanding its coverage.

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For the OHTAC decision-making process concerning potential changes in IVF funding, three aspects of IVF treatment were examined: clinical effectiveness of the procedure in patients with infertility other than tubal obstruction; cost-effectiveness of IVF compared to alternative treatments; and role of IVF in reducing multiple pregnancy rates. The analysis reviewed existing indications for IVF based on new advances in the technology and possible impacts on policy.

OHTAC Findings:

A systematic review, analysis and critical appraisal of the published literature by MAS found the following:

- In patients with idiopathic infertility and mild to moderate male factor infertility there were no statistically significant differences between IVF and IUI in terms of pregnancy and live births rates.
- However, when standard IVF was compared to ICSI in patients with moderate male factor infertility, ICSI resulted in almost twice as high fertilization rates when compared to standard IVF. Furthermore, according to expert opinion, ICSI might be the only effective treatment for severe male factor infertility.
- Review of cost-effectiveness studies showed that due to its relatively high cost, IVF should not be recommended as the first line of treatment in the majority of cases. Two important exceptions, however, are bilateral tubal obstruction and severe male factor infertility, where IVF should be offered immediately.
- IVF with single embryo transfer (SET) was shown to result in almost complete elimination of multiple pregnancies. At the same time, SET also leads to lower birth rates compared to IVF cycles when more than one embryo are transferred, resulting in higher cost per birth with SET. This limitation of IVF-SET could be overcome with the use of frozen embryos for cycles following the first attempt, which results in satisfactory cumulative birth rates.
- Based on results of literature review and consultations with experts, four categories of infertile patients who may benefit from additional IVF/ICSI

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coverage were identified. They include: (1) patients with severe male factor infertility, where IVF should be offered in conjunction with ICSI; (2) infertile women with serious medical contraindications to multiple pregnancy, who should be offered IVF-SET; (3) infertile patients who want to avoid the risk of multiple pregnancy and therefore opt for IVF-SET and [4] patients who failed treatment with IUI and wish to try IVF. However, since in the case of IVF following failed IUI, there has been no significant change in the technology in recent years which would alter existing provincial policy, the latter indication was not considered.

- An Ontario-based economic analysis compared the cost per birth using three treatment strategies: IUI, IVF-SET, and IVF with double embryo transfer (DET). Even after accounting for cost-savings due to avoidance of multiple pregnancies (short-term complications only), IVF-SET was still associated with the highest cost per birth. Approximate budget impact to cover the three possible indications for IVF listed above is estimated at \$9.8-\$12.8 million. Coverage of only first two indications, namely, ICSI in patients with severe male factor infertility and infertile women with serious medical contraindications to multiple pregnancy, is forecast to be \$3.8-\$5.5 millions.

OHTAC Recommendations:

OHTAC makes the following recommendations regarding changes in IVF funding:

- There are two indications where OHTAC recommends additional access to IVF: [1] IVF/ICSI for patients with severe male factor infertility; and [2] IVF-SET in infertile women with serious medical contraindications to multiple pregnancy.
- The Society of Obstetricians and Gynecologists of Canada and Canadian Urological Association should be asked to develop the set of parameters that clearly define the severe male factor infertility as well as a list of maternal medical conditions where multiple pregnancy is absolutely contraindicated.
- Couples who wish to avoid the risk of multiple pregnancy could consider IVF SET as an option to IUI, which is currently covered by OHIP.

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These recommendations will be disseminated to the health system through their posting on OHTAC's website and the distribution of OHTAC's E-bulletin.