Reproductive Techniques

Policy Number: 4.02.04  Last Review: 12/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for assisted reproductive technology (ART) when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Coverage of infertility treatment using assisted reproductive technology is a contract-specific benefit issue. Where benefits are available, all of the services identified by the CPT codes listed below might be considered eligible benefits unless indicated as being investigational.

Some contracts that cover ART treatment may have different member co-pay formulas and limits on these services than for other medical-surgical coverage.

The following reproductive techniques are considered **medically necessary;**
- cryopreservation of testicular tissue in adults with azoospermia as part of an intracytoplasmic sperm injection procedure;
- intracytoplasmic sperm injection for infertility;
- blastocyst transfer

The following lists summarize the CPT codes used to describe ART. Those procedures performed in order to **diagnose** infertility, i.e. laparoscopy and semen analysis, are **not** included in this review. Not all steps are routinely done in each case.

Procedures performed on the patient

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>55400</td>
<td>Vasovasostomy, vasovasorrhaphy (i.e., repair of prior vasectomy)</td>
</tr>
<tr>
<td>54800</td>
<td>Biopsy of epididymis (may be used to describe epididymal aspiration of sperm in men with obstructive or non-obstructive azoospermia or severe oligospermia)</td>
</tr>
<tr>
<td>54500</td>
<td>Biopsy of testis, needle (may be used to describe testicular aspiration of sperm for same indications as above)</td>
</tr>
<tr>
<td>54505</td>
<td>Biopsy of testis, incisional (separate procedure)</td>
</tr>
<tr>
<td>55870</td>
<td>Electroejaculation Electroejaculation (may be used in patients who are unable to produce</td>
</tr>
</tbody>
</table>
a normal ejaculate due to spinal cord or other nervous system disorder, i.e., diabetic neuropathy

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>58321</td>
<td>*Artificial insemination, intracervical</td>
</tr>
<tr>
<td>58322</td>
<td>*Artificial insemination, intrauterine</td>
</tr>
<tr>
<td>58970</td>
<td>Follicle puncture for oocyte retrieval, any method</td>
</tr>
<tr>
<td>58974</td>
<td>Embryo transfer, intrauterine</td>
</tr>
</tbody>
</table>

* Either intracervical or intrauterine artificial insemination may be performed where there is poor quality cervical mucus, anatomic factors, poor sperm quality or quantity, poor postcoital tests.

### In Vitro Laboratory Procedures:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>58323</td>
<td>Sperm washing for artificial insemination</td>
</tr>
<tr>
<td>58970</td>
<td>Follicle puncture for oocyte retrieval, any method</td>
</tr>
<tr>
<td>58974</td>
<td>Embryo transfer, intrauterine</td>
</tr>
<tr>
<td>58976</td>
<td>Gamete, zygote, or embryo intrafallopian transfer, any method</td>
</tr>
<tr>
<td>89240</td>
<td>Unlisted miscellaneous pathology test (this code should be used for cryopreservation of ovarian tissue or oocytes)</td>
</tr>
<tr>
<td>89250</td>
<td>Culture of oocytes(s)/embryo(s), less than 4 days. This CPT code originally described both the culture and fertilization of oocytes, but has been revised to describe only the culture step; the insemination step is now described separately in new CPT code 89268. Note also that this code is limited to culture of less than 4 days. New CPT code 89272 now describes culturing for longer than 4 days.</td>
</tr>
<tr>
<td>89251</td>
<td>Culture of oocyte(s)/embryo(s); with co-culture of oocyte(s)/embryos</td>
</tr>
<tr>
<td>89253</td>
<td>Assisted embryo hatching, any method. Assisted hatching is a technique performed to enhance the likelihood that the transferred embryo will implant in the uterus and establish a viable pregnancy. The technique involves in vitro disruption of the zona pellucida surrounding the embryo so that the embryo can “escape” and implant into the uterine wall. Assisted hatching has also been referred to as zona drilling and partial zonal dissolution. Assisted hatching is commonly performed as part of an IVF procedure in women over 40 who have a decreased incidence of implantation after embryo transfer and in women with prior failed IVF cycles due to failed implantation.</td>
</tr>
<tr>
<td>89254</td>
<td>Oocyte identification from follicular fluid. As part of the oocyte retrieval procedure (58970), follicular fluids are provided to the laboratory. Using microscopic examination and dissection, the oocytes are identified, isolated, classified, and placed in the culture environment. Prior to the introduction of the new CPT code 89254, this laboratory component of the oocyte retrieval process may have been coded as 89399.</td>
</tr>
<tr>
<td>89255</td>
<td>Preparation of embryo for transfer. Embryos resulting from ART techniques must be evaluated microscopically for stage of development, cell number, and quality to select the optimal embryo(s) for transfer. The selected embryos are loaded into an embryo transfer catheter, which is introduced by a physician into a patient’s uterus or fallopian tubes. Following the transfer, the catheter is flushed, and the flushings are examined to determine if the embryos(s) have been successfully transferred.</td>
</tr>
<tr>
<td>89257</td>
<td>Sperm identification from aspirate. After aspiration of sperm from the epididymis or testis, the fluid undergoes immediate laboratory analysis so that the sperm can be identified and isolated. Prior to the introduction of 89257, this laboratory procedure may</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>89258</td>
<td>Cryopreservation; embryo. Cryopreservation involves moving the embryo through increasing concentrations of cryoprotectant and loading the embryo into straws or vials for subsequent freezing. The embryos are cooled gradually and then stored for as long as needed. It is estimated that about 20% of couples undergoing ART procedures would have embryos frozen. Prior to the introduction of 89258, this procedure probably would have been coded as 89399.</td>
</tr>
<tr>
<td>89259</td>
<td>Cryopreservation; sperm. Sperm are assessed for pre-freeze concentration and motility and viability, followed by addition of cryoprotectant agent. Aliquots are loaded into straws or vials, and the sample is cooled and stored. Cryopreservation is indicated for any diagnosis in which chemical or surgical castration is considered appropriate, or in other circumstances that preclude the collection of a semen sample on demand (i.e., paraplegia, ejaculatory dysfunction), following electroejaculation or sperm aspiration, prior to a vasectomy, or in situations in which the male must be absent for long periods of time (i.e., military service). Prior to the introduction of 89258, this procedure probably would have been coded as 89399.</td>
</tr>
<tr>
<td>89260</td>
<td>Sperm isolation; simple prep (see 89261)</td>
</tr>
<tr>
<td>89261</td>
<td>Sperm isolation; complex. Simple or complex sperm isolation may be performed prior to intrauterine insemination or IVF. The choice of simple or complex preparation is based on a prior semen analysis.</td>
</tr>
<tr>
<td>89264</td>
<td>Sperm identification from testis tissue, fresh or cryopreserved. This CPT code describes the dissection of biopsied testicular tissue (i.e., CPT codes 54500-54505) to identify and isolate sperm. This procedure would be typically done in a patient with male factor infertility as part of an intracytoplasmic sperm injection (ICSI) procedure.</td>
</tr>
<tr>
<td>89268</td>
<td>Insemination of oocytes. Insemination, or fertilization, used to be included in the original code 89250. However, in 2004, code 89250 was unbundled and separate codes were created for culture and insemination.</td>
</tr>
<tr>
<td>89272</td>
<td>Extended culture of oocyte(s) / embryo(s), 4-7 days. This new code is a companion code for 89250 (see above), which describes the length of culture. Culturing beyond 4 days allows the embryo to develop to the blastocyst stage.</td>
</tr>
<tr>
<td>89280</td>
<td>Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes</td>
</tr>
<tr>
<td>89281</td>
<td>Assisted oocyte fertilization, microtechnique; greater than 10 oocytes</td>
</tr>
<tr>
<td>89335</td>
<td>Cryopreservation, reproductive tissue, testicular. While cryopreservation of ejaculated sperm is the most common technique of preserving male gametes, in cases of azoospermia or where there is blockage of the epididymis, a testicular biopsy may be performed to harvest testicular tissue. Spermatozoa isolated from testicular tissue may then be used in a subsequent IVF procedure, using intracytoplasmic sperm injection. Since IVF is not immediately successful in many cases, additional sperm can be extracted from the cryopreserved tissues for subsequent cycles, thus eliminating the need for sequential testicular biopsies coinciding with the harvest of the oocyte.</td>
</tr>
<tr>
<td>89337</td>
<td>Cryopreservation, mature oocyte(s)</td>
</tr>
<tr>
<td>89342</td>
<td>Storage, (per year); embryo(s)</td>
</tr>
<tr>
<td>89343</td>
<td>Storage, (per year); sperm / semen</td>
</tr>
<tr>
<td>89344</td>
<td>Storage (per year); reproductive tissue, testicular/ovarian</td>
</tr>
<tr>
<td>89346</td>
<td>Storage (per year); oocyte(s)</td>
</tr>
<tr>
<td>89352</td>
<td>Thawing of cryopreserved; embryo(s)</td>
</tr>
<tr>
<td>89353</td>
<td>Thawing of cryopreserved; sperm / semen, each aliquot</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>89354</td>
<td>Thawing of cryopreserved; reproductive tissue, testicular/ovarian</td>
</tr>
<tr>
<td>89356</td>
<td>Thawing of cryopreserved; oocytes, each aliquot</td>
</tr>
<tr>
<td>0058T</td>
<td>Cryopreservation; reproductive tissue, ovarian</td>
</tr>
<tr>
<td>S4011</td>
<td>In vitro fertilization; including but not limited to identification and incubation of mature oocytes, fertilization with sperm, incubation of embryo(s), and subsequent visualization for determination of development</td>
</tr>
<tr>
<td>S4013</td>
<td>Complete cycle, gamete intrafallopian transfer (GIFT), case rate</td>
</tr>
<tr>
<td>S4014</td>
<td>Complete cycle, zygote intrafallopian transfer (ZIFT), case rate</td>
</tr>
<tr>
<td>S4015</td>
<td>Complete in vitro fertilization cycle, not otherwise specified, case rate</td>
</tr>
<tr>
<td>S4016</td>
<td>Frozen in vitro fertilization cycle, case rate</td>
</tr>
<tr>
<td>S4017</td>
<td>Incomplete cycle, treatment cancelled prior to stimulation, case rate</td>
</tr>
<tr>
<td>S4018</td>
<td>Frozen embryo transfer procedure cancelled before transfer, case rate</td>
</tr>
<tr>
<td>S4020</td>
<td>In vitro fertilization procedure cancelled before aspiration, case rate</td>
</tr>
<tr>
<td>S4021</td>
<td>In vitro fertilization procedure cancelled after aspiration, case rate</td>
</tr>
<tr>
<td>S4022</td>
<td>Assisted oocyte fertilization, case rate</td>
</tr>
<tr>
<td>S4023</td>
<td>Donor egg cycle, incomplete, case rate</td>
</tr>
<tr>
<td>S4025</td>
<td>Donor services for in vitro fertilization (sperm or embryo), case rate</td>
</tr>
<tr>
<td>S4026</td>
<td>Procurement of donor sperm from sperm bank</td>
</tr>
<tr>
<td>S4027</td>
<td>Storage of previously frozen embryos</td>
</tr>
<tr>
<td>S4028</td>
<td>Microsurgical epididymal sperm aspiration (MESA)</td>
</tr>
<tr>
<td>S4030</td>
<td>Sperm procurement and cryopreservation services; initial visit</td>
</tr>
<tr>
<td>S4031</td>
<td>Sperm procurement and cryopreservation services; subsequent visit</td>
</tr>
<tr>
<td>S4035</td>
<td>Stimulated intrauterine insemination (IUI), case rate</td>
</tr>
<tr>
<td>S4037</td>
<td>Cryopreserved embryo transfer, case rate</td>
</tr>
<tr>
<td>S4040</td>
<td>Monitoring and storage of cryopreserved embryos, per 30 days</td>
</tr>
<tr>
<td>S4042</td>
<td>Management of ovulation induction (interpretation of diagnostic tests and studies, nonface-to-face medical management of the patient), per cycle</td>
</tr>
</tbody>
</table>

**When Policy Topic is not covered**

The following laboratory procedures are considered investigational:

- assisted hatching;
- co-culture of embryos;
- cryopreservation of ovarian tissue, or oocytes; cryopreservation of testicular tissue in prepubertal patients; storage and thawing of ovarian tissue, oocytes or testicular tissue
- intracytoplasmic sperm injection in the absence of infertility.

<table>
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</tr>
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<tbody>
<tr>
<td>89251</td>
<td>Culture and fertilization of oocytes less than 4 days; with co-culture of oocytes/embryos. Co-culture techniques involve tissue culture of human embryos in the presence of...</td>
</tr>
</tbody>
</table>
The procedure involves the isolation of the substrate cells, culture, plating, and co-culture of these cells with human embryos. The purpose of co-culture is to produce a more viable embryo at the blastocyst stage of development for subsequent transfer to the uterus. Co-culture is not routinely done as part of all IVF procedures; the technique may not be available in all infertility labs.

<table>
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<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>89335</td>
<td>Cryopreservation of testicular tissue in prepubertal boys.</td>
</tr>
<tr>
<td>89337</td>
<td>Cryopreservation, mature oocyte(s)</td>
</tr>
<tr>
<td>89342</td>
<td>Storage (per year); embryo(s)</td>
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</tbody>
</table>

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
  - With infertility |  
  - Interventions of interest are:  
    - In vitro fertilization with assisted hatching |  
  - Comparators of interest are:  
    - In vitro fertilization without assisted hatching |  
  - Relevant outcomes include:  
    - Health status measures  
    - Treatment-related morbidity |
| Individuals:  
  - With infertility |  
  - Interventions of interest are:  
    - In vitro fertilization with embryo co-culture |  
  - Comparators of interest are:  
    - In vitro fertilization without embryo co-culture |  
  - Relevant outcomes include:  
    - Health status measures  
    - Treatment-related morbidity |
| Individuals:  
  - With cancer who will undergo treatment that may lead to infertility |  
  - Interventions of interest are:  
    - Cryopreservation of ovarian tissue |  
  - Comparators of interest are:  
    - Cryopreservation of embryos  
    - No cryopreservation of ovarian tissue |  
  - Relevant outcomes include:  
    - Health status measures  
    - Treatment-related morbidity |
| Individuals:  
  - With cancer who will undergo treatment that may lead to infertility |  
  - Interventions of interest are:  
    - Cryopreservation of oocytes |  
  - Comparators of interest are:  
    - Cryopreservation of embryos  
    - No cryopreservation of ovarian tissue |  
  - Relevant outcomes include:  
    - Health status measures  
    - Treatment-related morbidity |
| Individuals:  
  - With infertility |  
  - Interventions of interest are:  
    - In vitro fertilization with blastocyst transfer |  
  - Comparators of interest are:  
    - In vitro fertilization with cleavage-stage transfer |  
  - Relevant outcomes include:  
    - Health status measures  
    - Treatment-related morbidity |
| Individuals:  
  - With male factor infertility |  
  - Interventions of interest are:  
    - In vitro fertilization with intracytoplasmic |  
  - Comparators of interest are:  
    - In vitro fertilization without intracytoplasmic sperm |  
  - Relevant outcomes include:  
    - Health status measures  
    - Treatment-related morbidity |
The policy addresses a variety of techniques available to establish a viable pregnancy for couples who have been diagnosed with infertility and for whom assisted insemination was unsuccessful.

For individuals who have infertility who receive in vitro fertilization (IVF) with assisted hatching, the evidence includes randomized controlled trials (RCTs), a systematic review, and a large observational study. Relevant outcomes are health status measures, resource utilization, and treatment-related morbidity. RCTs have not shown that assisted hatching improves the live birth rate compared with standard care. Findings on clinical pregnancy rate after assisted hatching were mixed but RCTs generally did not find improvement with assisted hatching versus standard care. A large observational study found that assisted hatching was associated with worse outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have infertility who receive IVF with embryo co-culture, the evidence includes a RCTs and case series. Relevant outcomes are health status measures, resource utilization, and treatment-related morbidity. Most clinical trials did not find improved implantation or pregnancy rate after co-culture, and studies have not reported the live birth rate. Moreover, co-culture techniques have not been standardized and 1 RCT that found a higher clinical pregnancy rate with co-culture than a standard practice control group used a novel technique that has not been otherwise evaluated. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who will undergo treatment that may lead to infertility who receive cryopreservation of ovarian tissue, the evidence includes case series. Relevant outcomes are health status measures, resource utilization, and treatment-related morbidity. The technique has not been standardized and there is a lack of controlled studies on health outcomes following cryopreservation of ovarian tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who will undergo treatment that may lead to infertility who receive cryopreservation of oocytes, the evidence includes RCTs and
a systematic review on the technique in related populations. Relevant outcomes are health status measures, resource utilization, and treatment-related morbidity. The systematic review found that fertilization rates ranged from 71% to 79%, and the clinical pregnancy rates per transfer ranged from 36% to 61%. The available studies are conducted in highly selected populations and may not be generalizable to the population of interest, women with cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have infertility who receive IVF with blastocyst transfer, the evidence includes RCTs and meta-analyses. Relevant outcomes are health status measures, resource utilization, and treatment-related morbidity. RCTs and meta-analyses have found that blastocyst transfer is associated with higher live birth rates compared with cleavage stage transfer. One meta-analysis found a significantly higher rate of preterm birth after blastocyst stage versus cleavage stage transfer, but not find increased risks of other outcomes such as low birth rate and perinatal mortality. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have male factor infertility who receive IVF with intracytoplasmic sperm injection (ICSI), the evidence includes observational studies and a systematic review. Relevant outcomes are health status measures, resource utilization, and treatment-related morbidity. No RCTs are available. Observational studies, which are subject to limitations (eg, selection bias), have found similar rates of clinical pregnancy and live birth after ICSI and standard IVF, and a meta-analysis of observational studies found a higher rate of genitourinary malformations in children born after ICSI but only when lower quality studies were included in the analysis. RCTs comparing health outcomes after ICSI for male factor infertility and standard IVF are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input was obtained in 2012, and there was general agreement among reviewers that ICSI in men with male infertility factor was considered medically necessary.

For individuals who have azoospermia who receive cryopreservation of testicular tissue as part of ICSI, the evidence includes no clinical trials. Relevant outcomes are health status measures, resource utilization, and treatment-related morbidity. Cryopreservation of testicular tissue in adult men with azoospermia is a well-established component of the ICSI procedure. However, there is a lack of clinical trials. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input was obtained in 2012 and there was general agreement among reviewers that cryopreservation of testicular tissue in adult men with azoospermia was considered medically necessary.
For individuals who are prepubertal boys with cancer who receive cryopreservation of testicular tissue, the evidence includes no clinical trials. Relevant outcomes are health status measures, resource utilization, and treatment-related morbidity. No clinical trials were identified evaluating the safety and efficacy of cryopreservation of testicular tissue in prepubertal boys undergoing cancer therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**
Infertility can be due either to female factors (i.e., pelvic adhesions, ovarian dysfunction, endometriosis, prior tubal ligation), male factors (i.e., abnormalities in sperm production, function, or transport or prior vasectomy), a combination of both male and female factors, or unknown causes.

Various reproductive techniques are available to establish a viable pregnancy; different techniques are used depending on the reason for infertility. Assisted reproductive technologies (ART), as defined by the Centers for Disease Control (CDC) and other organizations, refers to fertility treatments in which both the eggs and sperm are handled. Not included in ART is assisted insemination (artificial insemination) using sperm from either a woman’s partner or a sperm donor. In most instances ART will involve in vitro fertilization (IVF), a procedure in which oocytes harvested from the female are inseminated in vitro with sperm harvested from the male. Following the fertilization procedure, the zygote is cultured and ultimately transferred back into the female’s uterus or fallopian tubes. In some instances, the oocyte and sperm are collected, but no in vitro fertilization takes place, and the gametes are reintroduced into the fallopian tubes. Examples of ART include, but are not limited to, gamete intrafallopian transfer (GIFT), transuterine fallopian transfer (TUFT), natural oocyte retrieval with intravaginal fertilization (NORIF), pronuclear state tubal transfer (PROST), tubal embryo transfer (TET), zygote intrafallopian transfer (ZIFT), gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy.

The various components of ART and implantation into the uterus can be broadly subdivided into oocyte harvesting procedures, which are performed on the female partner; sperm collection procedures, which are performed on the male partner; and the in vitro component, i.e., the laboratory procedures, which are performed on the collected oocyte and sperm. The final step is the implantation procedure.

The majority of CPT codes describing the various steps in ART procedures are longstanding techniques. This includes codes for oocyte retrieval, sperm isolation, culture and fertilization of the oocyte, and embryo; zygote; or gamete transfer into the uterus or fallopian tubes. Only the relatively new reproductive techniques (i.e., intracytoplasmic sperm injection, assisted hatching, co-culture of embryos) and cryopreservation of reproductive tissue (i.e., testicular, ovarian, or oocytes) will be considered.

**Regulatory Status**
There are no medical devices or diagnostic tests related to assisted reproductive techniques that require FDA approval or clearance.
**Rationale**
This evidence review was created in April 1998 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was conducted through June 7, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Assisted Hatching**
Implantation of the embryo in the uterus is a key component of success with in vitro fertilization (IVF). Although the exact steps in implantation are poorly understood, normal rupture of the surrounding zona pellucida with escape of the developing embryo (termed hatching) is crucial. Mechanical disruption of the zona pellucida (ie, assisted hatching) has been proposed as a mechanism to improve implantation rates.

**Clinical Context and Therapy Purpose**
The purpose of IVF with assisted hatching in patients with infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does IVF with assisted hatching treat infertility and improve the net health outcome?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population of interest is patients who are infertile.

Interventions
The therapy being considered is IVF with assisted hatching.

Comparators
The following practice is currently being used to make decisions about infertility: IVF without assisted hatching.

Outcomes
The general outcomes of interest are live birth rates and infant abnormalities.

Timing
Follow-up is measured in weeks to confirm a successful pregnancy and months to confirm a successful birth.

Setting
Patients with infertility are actively managed by gynecologists, endocrinologists, and primary care providers in an outpatient setting.

Systematic Reviews
A Cochrane review and meta-analysis by Carney et al (2012) identified 31 RCTs evaluating assisted hatching (total N=5728 individuals).\textsuperscript{1} Twelve studies included women with a poor fertility prognosis, 12 studies included women with a good fertility prognosis, and the remaining 7 studies did not report this factor. Fifteen studies used a laser for assisted hatching, 11 used chemical means, and 5 used mechanical means. Live birth rates were reported in 9 studies (n=1921 women). A pooled analysis of data from the 9 studies did not find a statistically significant difference between the groups receiving assisted hatching and a control condition (odds ratio [OR], 1.03; 95% confidence interval [CI], 0.85 to 1.26). The rate of live birth was 313 (31%) of 995 in the assisted hatching group and 282 (30%) of 926 in the control group. All 31 trials reported clinical pregnancy rates. In a meta-analysis of all trials, assisted hatching improved the pregnancy rate, but the estimate for the odds was marginally statistically significant (OR=1.13; 95% CI, 1.01 to 1.27).

Randomized Controlled Trials
Two RCTs not assessed in the Cochrane review have compared laser-assisted hatching with the standard of care. Shi et al (2016) evaluated 178 patients of advanced maternal age (age range, 35-42 years).\textsuperscript{2} There were no statistically significant differences in implantation rates (32.5% in the assisted hatching group vs 39.3% in the control group) or in clinical pregnancy rates (48.8% in the assisted hatching group vs 50.4% in the control group; p values not reported). Kanyo et al (2016) assessed 413 women (mean age, 33 years).\textsuperscript{3} In the overall study population, there was no statistically significant difference in the clinical pregnancy rate between the assisted hatching group (33.3%) and the control group (27.4%; p=0.08). However, in the subgroup of patients ages 38 or older,
the clinical pregnancy rate was significantly higher in the assisted hatching group (18.4%) than in the control group (11.4%; \( p=0.03 \)). There was no significant between-group difference in clinical pregnancy rate among women younger than 38 years old. The age groupings (ie, <38 years vs ≥38 years) were not specifically discussed as a prespecified subgroup analysis. Neither trial reported live birth rates.

**Retrospective Studies**

Knudtson et al (2017), in a retrospective cohort study, analyzed live birth rates in women who underwent first-cycle, autologous frozen embryo transfer.\(^4\) From data reported between 2004 and 2013 to the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System, 151,533 cycles were identified, 70,738 (46.7%) with assisted hatching and 80,795 (53.3%) without. Assisted hatching had a significantly lower live birth rate (34.2%) than nonassisted hatching (35.4%; \( p<0.001 \)). Also, older patients (age ≥38 years) who received assisted hatching were associated with lower live birth rates (\( p≤0.05 \)). The study was limited by the retrospective nature of the database, incomplete data, and the inability due to deidentification to link thawed cycles to original retrieval and insemination techniques.

Kissin et al (2014) retrospectively reviewed data on assisted hatching in the United States from 2000 to 2010.\(^5\) Data were taken from the Centers for Disease Control and Prevention’s National Assisted Reproductive Technology Surveillance System. The analysis of outcomes was limited to fresh autologous IVF cycles for which a transfer was performed on day 3 or 5. For the total patient population (\( N=536,852 \)), rates of implantation, clinical pregnancy, and live births were significantly lower when assisted hatching was used. For example, the live birth rate was 28.3% with assisted hatching and 36.5% without (adjusted odds ratio [AOR], 0.75; 95% CI, 0.70 to 0.81). Moreover, the rate of miscarriage was significantly higher when assisted hatching was used (18.0% vs 13.5%; AOR=1.43; 95% CI, 1.34 to 1.52).

**Section Summary: Assisted Hatching**

The available literature has generally not found better outcomes with assisted hatching than with standard of care. A 2012 Cochrane review of heterogeneous RCTs found that clinical pregnancy rates but not the live birth rates improved with assisted hatching. In subsequent RCTs, laser-assisted hatching did not improve the clinical pregnancy rate but, in 1 study, there was a higher rate of clinical pregnancy in the subgroup of women 38 years or older. In addition, analysis of a large national database found better outcomes (eg, clinical pregnancy and live birth rates) when assisted hatching was not used.

**Embryo Co-Culture**

In routine IVF procedures, the embryo is transferred to the uterus on day 2 or 3 of development, when it has between 4 and 8 cells. Embryo co-culture techniques, used successfully in domestic animals, represent an effort to improve the culture media for embryos such that a greater proportion of embryos will reach the blastocyst-stage, in an attempt to improve implantation and pregnancy rates. In
addition, if co-culture results in a higher implantation rate, fewer embryos could be transferred in each cycle, decreasing the incidence of multiple pregnancies. A variety of co-culture techniques have been investigated involving the use of feeder cell layers derived from a range of tissues, including the use of human reproductive tissues (ie, oviducts) to nonhuman cells (ie, fetal bovine uterine or oviduct cells) to established cell lines (ie, Vero cells or bovine kidney cells).

**Clinical Context and Therapy Purpose**
The purpose of IVF with embryo co-culture in patients with infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does IVF with embryo co-culture to treat infertility improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is patients who are infertile.

**Interventions**
The therapy being considered is IVF with embryo co-culture.

**Comparators**
The following practice is currently being used to make decisions about infertility: IVF without embryo co-culture.

**Outcomes**
The general outcomes of interest are live birth rates and infant abnormalities.

**Timing**
Follow-up is measured in weeks to confirm a successful pregnancy and months to confirm a successful birth.

**Setting**
Patients with infertility are actively managed by gynecologists, endocrinologists, and primary care providers in an outpatient setting.

**Randomized Controlled Trials**
Currently, no standardized method of co-culture has emerged, and clinical trials have generally not found that co-culture is associated with an improved implantation or pregnancy rates. For example, Wetzels et al (1998) reported on an RCT that assigned IVF treatments to co-culture with human fibroblasts or no culture. Patients in the 2 groups were stratified by age (older or younger than 36 years) and prior IVF attempts (yes vs no). The trialists reported that fibroblast co-culture did not affect the implantation or pregnancy rates. More recently, Ohl et al (2015) reported on a novel co-culture technique involving autologous endometrial cell co-culture. In an interim analysis of 320 patients, the clinical pregnancy rate
per embryo transfer was significantly higher in the co-culture group (53.4%) than in the control group (37.3%; p=0.025).

**Section Summary: Embryo Co-Culture**
There is no standardized method of co-culture, and few clinical trials have evaluated outcomes. Most have not found improved implantation or pregnancy rates after co-culture. A 2015 RCT has reported on a novel co-culture method and an interim analysis of the trial found a higher clinical pregnancy rate with co-culture than with standard practice control group. Additional studies are needed to evaluate this novel co-culture technique. No studies have reported on the impact of co-culture on live birth rates.

**Cryopreservation of Ovarian Tissue**

**Clinical Context and Therapy Purpose**
The purpose of cryopreservation of ovarian tissue in patients with cancer who will undergo treatment that could precipitate infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the cryopreservation of ovarian tissue treat infertility and improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is cancer patients who undergo treatment that could precipitate infertility.

**Interventions**
The therapy being considered is cryopreservation of ovarian tissue.

**Comparators**
The following practice is currently being used to make decisions about infertility: cryopreservation of embryos, but not of ovarian tissue.

**Outcomes**
The general outcomes of interest are live birth rates and infant abnormalities.

**Timing**
Follow-up is measured in weeks to confirm a successful pregnancy and months to confirm a successful birth.

**Setting**
Patients with cancer who will undergo treatment that might lead to infertility are actively managed by an oncologist, gynecologists, endocrinologists, and primary care providers in an outpatient setting.
Case Series
Cryopreservation of ovarian tissue or an entire ovary with subsequent auto- or heterotopic transplant has been investigated as a technique to sustain the reproductive function of women or children who are faced with sterilizing procedures, such as chemotherapy, radiotherapy, or surgery, frequently due to malignant diseases. There are a few case reports assessing the return of ovarian function using this technique.\textsuperscript{13,14} There are also case series describing live births using cryopreserved ovarian tissue.\textsuperscript{15-17} However, in general, the technique is not standardized and insufficiently studied to determine the success rate.\textsuperscript{18,19} Johnson and Patrizio (2011) commented on whole ovary freezing as a fertility preservation technique in women with disease or disease treatment that threatens their reproductive tract function.\textsuperscript{20} They concluded: “Although theoretically optimal from the point of view of maximal follicle protection and preservation, the risks and difficulties involved in whole ovary freezing limit this technique to experimental situations.”

Section Summary: Cryopreservation of Ovarian Tissue
As a technique, cryopreservation of ovarian tissue has not been standardized, and there are insufficient published data that this reproductive technique is effective and safe.

Cryopreservation of Oocytes
Cryopreservation of oocytes has been examined as a fertility preservation option for reproductive-age women undergoing cancer treatment. The mature oocyte is very fragile due to its large size, high water content, and chromosomal arrangement. For example, the mature oocyte is arrested in meiosis, and as such, the chromosomes are aligned in a meiotic spindle. This spindle is easily damaged in freezing and thawing. Survival after thawing may also be associated with sublethal damage, which may further impact on the quality of the subsequent embryo. Moreover, due to a large amount of water when the oocyte is frozen, ice crystals may form that can damage the integrity of the cell. To reduce or prevent ice crystals, oocytes are dehydrated using cryoprotectants, which replace the water in the cell. There are 2 primary approaches to cryopreservation: a controlled-rate slow-cooling method and a flash-freezing process known as vitrification. Vitrification, the newer method, is faster and requires a higher concentration of cryoprotectants.

Clinical Context and Therapy Purpose
The purpose of cryopreservation of oocytes in cancer patients who will undergo treatment that might precipitate infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the cryopreservation of oocytes treat infertility improve and the net health outcome?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population of interest is cancer patients who undergo treatment that might precipitate infertility.

Interventions
The therapy being considered is cryopreservation of oocytes.

Comparators
The following practice is currently being used to make decisions about infertility: cryopreservation of embryos, but not of ovarian tissue.

Outcomes
The general outcomes of interest are live birth rates and infant abnormalities.

Timing
Follow-up is measured in weeks to confirm a successful pregnancy and months to confirm a successful birth.

Setting
Patients with cancer who will undergo treatment that may lead to infertility are actively managed by an oncologist, gynecologists, endocrinologists, and primary care providers in an outpatient setting.

Systematic Reviews
The American Society for Reproductive Medicine and Society for Assisted Reproductive Technology (2013) updated their joint guidelines on mature oocyte cryopreservation. A systematic review of the literature, conducted as part of guideline development, identified 4 RCTs comparing outcomes of assisted reproduction with cryopreserved and fresh oocytes. All trials were conducted in Europe and none among patients who desired to preserve fertility after medical treatment (eg, chemotherapy). In these studies, fertilization rates ranged from 71% to 79%, and the clinical pregnancy rates per transfer ranged from 36% to 61%. The largest RCT (N=600) cited in the guidelines was published by Cobo et al (2010) in Spain. This trial included oocyte recipients between 18 and 49 years of age who had failed fewer than 3 previous IVF attempts. The primary outcome was the ongoing pregnancy rate; this was defined as the presence of at least 1 viable fetus 10 to 11 weeks after embryo transfer. In an intention-to-treat analysis, the ongoing pregnancy rate was 43.7% in the vitrification group and 41.7% in the fresh oocyte group. Vitrification was considered noninferior to fresh oocyte transfer according to a prespecified margin of difference. The guidelines noted that the available data might not be generalizable to the United States, to clinics with less experience with these techniques, or to other populations (eg, older women, cancer patients). The authors stated that data from the United States are available only from a few clinics and report on young highly select populations. Pregnancy outcomes and rates of congenital anomalies were not discussed.
Observational Studies
After the American Society for Reproductive Medicine and Society for Assisted Reproductive Technology guidelines were released, Levi Setti et al (2013) in Italy published an observational study.23 This study compared outcomes in pregnancies achieved with fresh or frozen oocytes. The investigators identified 855 patients in an Italian database who had become pregnant using fresh and/or cryopreserved and thawed oocytes. The authors did not state the reasons for a desire for fertility preservation. The 855 patients had a total of 954 clinical pregnancies; 197 were obtained with frozen oocytes and 757 with fresh oocytes. There were 687 pregnancies from fresh cycle oocytes only, 129 pregnancies with frozen oocytes only, and 138 pregnancies from both fresh and frozen oocyte cycles. The live birth rate was 68% (134/197) from frozen and thawed oocytes and 77% (584/757) fresh oocyte cycles. The live birth rate was significantly higher after fresh cycle oocytes (p=0.008).

Section Summary: Cryopreservation of Oocytes
There are insufficient published data on the safety and efficacy of cryopreservation of oocytes; and data are only available from select clinical settings, generally outside of the United States. Moreover, there is a lack of published data on success rates with cryopreserved oocytes in women who froze oocytes because they were undergoing chemotherapy. Data on health outcomes (eg, clinical pregnancy rate, live birth rate) in the population of interest are needed.

Blastocyst Transfer
The most common days for embryo transfer in the clinical IVF setting are day 3 or day 5. Embryo transfer at the blastocyst-stage on day 5 continues to be less common than cleavage-stage transfer on day 3. First introduced in clinical practice in 2005, use of blastocyst transfer is increasing in clinical practice. The rationale and reported advantages for blastocyst transfer are: higher implantation and clinical pregnancy rates, a more viable option for limiting to single embryo transfer, more appropriate endometrium-embryo synchronicity, optimization of embryo selection due to embryo development progression, and decreased potential for embryo trauma with biopsy obtained for preimplantation genetic testing. Advances in cell culture techniques and embryology assessments have facilitated an increased use of blastocyst transfer and research into the technique. Critics of blastocyst transfer have raised concerns about the limitation on the number of available embryos for transfer once the cleavage-stage is passed; critics also cite concerns due to uncertainties about the effects of the culture microenvironment, as well as early indicators of a higher rate of adverse pregnancy outcomes.

Clinical Context and Therapy Purpose
The purpose of IVF with blastocyst transfer in patients with infertility is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does IVF with blastocyst transfer treat infertility and improve the net health outcome?
The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is patients who are infertile.

**Interventions**
The therapy being considered is IVF with blastocyst transfer.

**Comparators**
The following practice is currently being used to make decisions about infertility: IVF without cleavage-stage transfer.

**Outcomes**
The general outcomes of interest are live birth rates and infant abnormalities.

**Timing**
Follow-up is measured in weeks to confirm a successful pregnancy and months to confirm a successful birth.

**Setting**
Patients with infertility are actively managed by gynecologists, endocrinologists, and primary care providers in an outpatient setting.

**Systematic Reviews**
Several systematic reviews of studies comparing outcomes associated with blastocyst-stage transfer with those of earlier stage transfer have been published. Only the Cochrane review by Glu jovsky et al (2012) included RCTs. They identified 23 RCTs, 12 of which reported on the rates of live births per couple. A pooled analysis of these trials found a significantly higher live birth rate with blastocyst transfer (292/751 [39%]) than with cleavage-stage transfer (237/759 [31%]). The odds for live birth was 1.40 (95% CI, 1.13 to 1.74). There was no significant difference in the rate of multiple pregnancies between the 2 treatment groups (16 RCTs; OR=0.92; 95% CI, 0.71 to 1.19). In addition, there was no significant difference in the miscarriage rate (14 RCTs; OR=1.14; 95% CI, 0.84 to 1.55). Glu jovsky et al (2016), in their updated Cochrane review, placed more emphasis on whether blastocyst-stage (day 5-6) embryo transfers improved the live birth rates, and other associated outcomes, compared with cleavage-stage (day 2-3) embryo transfers. Data from 4 new studies, 3 of which were published studies and resulted in a total of 27 parallel-design RCTs that included 4031 couples or women. The data from a fourth study was only available in abstract form and reported on outcomes from a multicenter trial comparing blastocyst with day 2-3 transfer in intracytoplasmic sperm injection (ICSI) cycles for male factor infertility. There were no exclusions from the 2012 review. The live birth rate following fresh transfer was higher in the blastocyst transfer group (OR=1.48; 95% CI, 1.20 to 1.82; 13 RCTs, 1630 women, I²=45%, low-quality evidence). There was no evidence of a difference between groups in rates of cumulative pregnancy per couple following fresh and frozen-thawed transfer after 1 oocyte
retrieval (OR=0.89; 95% CI, 0.64 to 1.22; 5 RCTs, 632 women, $I^2=71\%$, very low quality evidence). The clinical pregnancy rate was also higher in the blastocyst transfer group, following fresh transfer (OR=1.30; 95% CI, 1.14 to 1.47; 27 RCTs, 4031 women, $I^2=56\%$, moderate-quality evidence). Embryo freezing rates were lower in the blastocyst transfer group (OR=0.48; 95% CI, 0.40 to 0.57; 14 RCTs, 2292 women, $I^2=84\%$, low-quality evidence). Failure to transfer any embryos was higher in the blastocyst transfer group (OR=2.50; 95% CI, 1.76 to 3.55; 17 RCTs, 2577 women, $I^2=36\%$, moderate-quality evidence). The data for rates of multiple pregnancy and miscarriage were incomplete in 70% of the trials and limit conclusions concerning the following findings. There was no evidence of a difference between the groups in rates of multiple pregnancies (OR=1.05, 95% CI, 0.83 to 1.33; 19 RCTs, 3019 women, $I^2=30\%$, low-quality evidence) or miscarriages (OR=1.15, 95% CI, 0.88 to 1.50; 18 RCTs, 2917 women, $I^2=0\%$, low-quality evidence). Reviewers reported that the main limitation of the RCTs assessed was a high risk of bias, which was associated with failure to describe acceptable methods of randomization and unclear or high risk of attrition bias.

Maheshwari et al (2013) identified 8 observational studies analyzing singleton births following embryo transfer at the blastocyst or cleavage stage and reporting obstetric and/or perinatal outcomes. Meta-analysis of 6 studies found a significantly higher rate of preterm delivery at less than 37 weeks after blastocyst-stage transfer compared with cleavage-stage transfer (relative risk, 1.27; 95% CI, 1.22 to 1.31); the absolute increase in risk was 2% (95% CI, 1% to 4%). Other pooled analyses of 2 to 3 studies each did not find significantly increased rates of low birth weight less than 1500 grams, congenital anomalies, or perinatal mortality following blastocyst-stage vs cleavage-stage embryo transfer.

**Observational Studies**

A retrospective cohort study by Kallen et al (2010) reported on risks associated with blastocyst transfer. Data were taken from the Swedish Medical Birth Register. There were 1311 infants born after blastocyst transfer and 12,562 born after cleavage-stage transfer. There were no significant differences in the rates of multiple births (10% after blastocyst transfer vs 8.9% after cleavage-stage transfer). Among singleton births, the rate of preterm birth (<32 weeks) was 1.7% (18/1071) in the blastocyst transfer group and 1.35% (142/10513) in the cleavage-stage transfer group. In a multivariate analysis controlling for year of birth, maternal age, parity, smoking habits, and body mass index, the AOR was 1.44 (95% CI, 0.87 to 2.40). The rate of low birth weight singletons (<1500 g or <2500 g) did not differ significantly between the blastocyst transfer group and the cleavage-stage transfer group. There was a significantly higher rate of relatively severe congenital malformation (eg, spina bifida, cardiovascular defects, cleft palate) after blastocyst transfer (61/1311 [4.7%]) than after cleavage-stage transfer (509/12,562 [4.1%]; AOR=1.33; 95% CI, 1.01 to 1.75). The groups did not differ significantly in their rates of low Appearance, Pulse, Grimace, Activity and Respiration scores, intracranial hemorrhage rates, respiratory diagnoses, or cardiovascular malformations. Respiratory diagnoses were given to 94 (7.2%) of 1311 infants born after blastocyst transfer and to 774 (6.2%) of 12,562 after cleavage-stage transfer (OR=1.15; 95% CI, 0.90 to 1.47).
Ginström Ernstad et al (2016) published another retrospective registry cohort study using data crosslinked across the Swedish Medical Birth Register, the Register of Birth Defects, and the National Patient Register. All singleton deliveries after blastocyst transfer in Sweden from 2002 through 2013 were compared with deliveries after cleavage-stage transfer and deliveries after spontaneous conception. There were 4819 singletons born after blastocyst transfer, 25,747 after cleavage-stage transfer, and 1,196,394 after spontaneous conception. Singletons born after blastocyst transfer had no increased risk of birth defects compared with singletons born after cleavage-stage transfer (AOR=0.94; 95% CI, 0.79 to 1.13) or spontaneous conception (AOR=1.09; 95% CI, 0.92 to 1.28). Perinatal mortality was higher in the blastocyst group vs the cleavage-stage group (AOR=1.61; 95% CI, 1.14 to 2.29). When comparing singletons born after blastocyst transfer with singletons born after spontaneous conception, a higher risk of preterm birth (<37 weeks) was detected (AOR=1.17; 95% CI, 1.05 to 1.31). Singletons born after blastocyst transfer had a lower rate of low birthweight (AOR=0.83; 95% CI, 0.71 to 0.97) than singletons born after cleavage-stage transfer. The rate of being small for gestational age was also lower in singletons born after blastocyst transfer than after both cleavage-stage conception (AOR=0.71; 95% CI, 0.56 to 0.88) and spontaneous conception (AOR=0.70; 95% CI, 0.57 to 0.87). The risks of placenta previa and placental abruption were higher in pregnancies after blastocyst transfer than in pregnancies after cleavage-stage (AOR=2.08; 95% CI, 1.70 to 2.55; AOR=1.62; 95% CI, 1.15 to 2.29, respectively) and after spontaneous conception (AOR=6.38; 95% CI, 5.31 to 7.66; AOR=2.31; 95% CI, 1.70 to 3.13, respectively).

**Section Summary: Blastocyst Transfer**
An updated 2016 Cochrane review of 27 RCTs compared the effectiveness of blastocyst transfers with cleavage-stage transfers. The primary outcomes of live birth and cumulative clinical pregnancy rates were higher with fresh blastocyst transfer. There were no differences between groups in multiple pregnancies or early pregnancy loss (miscarriage). The main limitation of the RCTs evaluated in the Cochrane review was a high risk of bias associated with failure to describe acceptable methods of randomization and unclear or high risk of attrition bias. Differences in outcomes with the use of cryopreserved blastocysts and cleavage-stage embryos have been reported, and the mechanisms are not well-understood. There are conflicting reports from retrospective studies on the incidence of pregnancy and neonatal adverse outcomes, including low birth weight and increased congenital anomalies.

**ICSI for Male Factor Infertility**
ICSI is performed in cases of male factor infertility (MFI) when either insufficient numbers of sperm, abnormal sperm morphology, or poor sperm motility preclude unassisted IVF. Fertilization rates represent an intermediate outcome; the final outcome is the number of pregnancies per initiated cycle or per embryo transfer.
Clinical Context and Therapy Purpose
The purpose of IVF with ICSI in patients with MFI is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does IVF with ICSI treat MFI and improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is men with MFI.

Interventions
The therapy being considered is IVF with ICSI.

Comparators
The following practice is currently being used to make decisions about infertility: IVF without ICSI.

Outcomes
The general outcomes of interest are live birth rates and infant abnormalities.

Timing
Follow-up is measured in weeks to confirm a successful pregnancy and months to confirm a successful birth.

Setting
Patients with MFI are actively managed by gynecologists, endocrinologists, and primary care providers in an outpatient setting.

Case Series
The number of pregnancies per cycle and per embryo transfers, reported in relatively large series published in the mid-1990s, ranged between 45% and 50%. At the time, those rates were very competitive with those of the standard IVF.

More recently, Borges et al (2017) retrospectively analyzed ICSI outcomes for patients with MFI compared with isolated tubal factor infertility (TFI). Nine hundred twenty-two ICSI cycles (743 for MFI, 179 for TFI) performed between 2010 and 2016 were identified. No significant differences were observed between the groups for rates of implantation (MFI=35.5% vs TFI=32%, p=0.34), pregnancy (MFI=46.9% vs TFI=40.9%, p=0.184), and miscarriage (MFI 10.3% vs TFI 10.6%, p=0.572); rates remained similar even after women were stratified into groups by age (≤35 years: MFI=531 vs TFI=112; >35 years: MFI=212 vs TFI=67). The study was limited by its retrospective design and by the fact that MFI severity could not be determined because patients were not categorized by diagnosis.
Boulet et al (2015) published a large retrospective analysis of the outcomes following ICSI vs standard IVF (data captured from the Centers for Disease Control and Prevention’s National Assisted Reproductive Technology Surveillance System from 2008 to 2012).38 During that time, there were data on 494,907 fresh IVF cycles. A total of 74.6% of cycles used ICSI, with 92.9% of the cycles involving MFI and 64.5% of the cycles not. Among couples with MFI, there was a statistically significantly lower rate of implantation after ICSI (25.5%) than after standard IVF (25.6%; p=0.02); however, this difference between groups was not clinically significant. Rates of clinical intrauterine pregnancy and live birth did not differ significantly between ICSI and standard IVF. In couples without MFI, implantation, clinical pregnancy, and live birth rates were all significantly higher with standard IVF than with ICSI.

**Adverse Events**
A systematic review and meta-analysis by Massaro et al (2015) examined adverse events related to ICSI and standard IVF without ICSI.39 Twenty-two observational studies were included; no RCTs were identified. Meta-analysis of 12 studies found a significantly increased odds of congenital genitourinary malformations in children conceived using ICSI vs standard IVF (pooled OR=1.27; 95% CI, 1.02 to 1.58; p=0.04; $I^2=0$). Five studies in this analysis were considered at high risk of bias, and a pooled analysis of the 4 studies considered at low risk of bias did not determine whether ICSI was associated with a statistically increased odds of genitourinary malformations.

**Section Summary: ICSI for Male Factor Infertility**
There is a lack of RCTs comparing ICSI with standard IVF. Observational studies have found similar rates of clinical pregnancy and live births after ICSI and standard IVF, but those observational studies are subject to limitations (eg, selection bias). A 2015 meta-analysis of observational studies found a significantly higher rate of congenital genitourinary malformations in children born after ICSI vs IVF, but there was no significant difference when only studies with low risk of bias were analyzed. RCTs comparing health outcomes after ICSI for MFI with standard IVF would strengthen the evidence base.

**Cryopreservation of Testicular Tissue in Adult Men With Azoospermia**
Testicular sperm extraction refers to the collection of sperm from testicular tissue in men with azoospermia. Extraction of testicular sperm may be performed during or subsequent to a diagnostic biopsy, specifically for the collection of spermatozoa. Spermatozoa may be isolated immediately and a portion used for an ICSI procedure during oocyte retrieval from the partner, with the remainder cryopreserved. Alternatively, the entire tissue sample can be cryopreserved with portion thawed and sperm isolation performed at subsequent ICSI cycles.

**Clinical Context and Therapy Purpose**
The purpose of the cryopreservation of testicular tissue as part of ICSI in patients with azoospermia is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The question addressed in this evidence review is: Does cryopreservation of testicular tissue as part of ICSI treat azoospermia and improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is men who are infertile.

**Interventions**
The therapy being considered is cryopreservation of testicular tissue as part of ICSI.

**Comparators**
The following practice is currently being used to make decisions about infertility: IVF without cryopreservation of testicular tissue.

**Outcomes**
The general outcomes of interest are live birth rates and infant abnormalities.

**Timing**
Follow-up is measured in weeks to confirm a successful pregnancy and months to confirm a successful birth.

**Setting**
Patients with azoospermia are actively managed by endocrinologists, primary care providers, and urologists in an outpatient setting.

**Case Series**
Testicular tissue extraction appears to be a well-established component of the overall ICSI procedure; cryopreservation of either the isolated sperm or the tissue sample eliminates the need for multiple biopsies to obtain fresh tissue in the event of a failed initial ICSI cycle. However, clinical trials evaluating health outcomes after cryopreservation of testicular tissue in adult men with azoospermia were not identified.

**Section Summary: Cryopreservation of Testicular Tissue in Adult Men With Azoospermia**
While cryopreservation of testicular tissue in adult men with azoospermia is a well-established component of the ICSI procedure, there is a lack of clinical trials to support this treatment.

**Cryopreservation of Testicular Tissue in Prepubertal Boys With Cancer**
A potential application of cryopreservation of testicular tissue is its potential to preserve the reproductive capacity in prepubertal boys undergoing cancer chemotherapy; cryopreservation of an ejaculate is not an option in these patients.
Clinical Context and Therapy Purpose
The purpose of the cryopreservation of testicular tissue in prepubertal boys with cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does cryopreservation of testicular tissue from prepubertal boys with cancer improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is prepubertal boys with cancer.

**Interventions**
The therapy being considered is the cryopreservation of testicular tissue.

**Comparators**
The following practice is currently being used to make decisions about infertility: no cryopreservation of testicular tissue.

**Outcomes**
The general outcomes of interest are live birth rates and infant abnormalities.

**Timing**
Follow-up is measured in weeks to confirm a successful pregnancy and months to confirm a successful birth.

**Setting**
Prepubertal boys with cancer are actively managed by endocrinologists, primary care providers, and urologists in an outpatient setting.

**Modeling Studies**
It has been hypothesized that reimplantation of the frozen-thawed testicular stem cells will reinitiate spermatogenesis or, alternatively, spermatogenesis could be attempted in vitro, using frozen-thaw spermatogonia. While these strategies have been explored in animals, there are inadequate human studies. 

**Section Summary: Cryopreservation of Testicular Tissue in Prepubertal Boys With Cancer**
No clinical trials were identified evaluating the safety and efficacy of cryopreservation of testicular tissue in prepubertal boys undergoing cancer therapy.

**Potential Adverse Events to Offspring Conceived Via Assisted Reproduction**
Systematic Reviews
Several systematic reviews have addressed the risk of birth defects. A systematic review by Kettner et al (2015) considered potential adverse events in children of various ages. Reviewers included controlled studies reporting at least 1 postnatal morbidity outcome in children who were and were not conceived using assisted reproductive. Twenty studies met the eligibility criteria; 30 were cohort studies, and 8 were case-control studies. There were no strong, consistent associations between use of reproductive techniques and childhood disease. For example, no statistically significant differences were found in rates of the following in children conceived spontaneously or with ART: chronic diseases (2 studies), cancer (3 studies), and allergic disease (5 studies). Findings were mixed on the risk of infectious and parasitic diseases. In the 8 studies examining this outcome, the odds varied between 0.37 and 5.7, and most results were not statistically significant. Rates of asthma or obstructive bronchitis were examined in 8 studies; 3 found significantly increased risk in children conceived by ART vs conceived spontaneously.

The review with the most data is that by Hansen et al (2013). They examined 45 cohort studies with outcomes in 92,671 infants born following assisted reproduction and 3,870,760 naturally conceived infants. In a pooled analysis, there was a higher risk of birth defects in infants born using reproductive techniques (relative risk, 1.32; 95% CI, 1.24 to 1.42). The risk of birth defects was also elevated when the analysis was limited to the 6 studies conducted in the United States or Canada (relative risk, 1.38; 95% CI, 1.16 to 1.64). Another review, published by Davies et al (2012), included data on 308,974 live births in Australia, 6163 of which used ART. There was a higher rate of birth defects after assisted conception (8.3%) compared with births to fertile women who did not use assisted reproduction (5.8%; unadjusted OR=1.47; 95% CI, 1.33 to 1.62). The risk of birth defects was still significantly elevated but was lower in an analysis that adjusted for other factors that might increase risk (eg, maternal age, parity, maternal ethnicity, maternal smoking during pregnancy, socioeconomic status; OR=1.28; 95% CI, 1.16 to 1.41).

Registry Studies
A Danish registry study by Bay et al (2013) addressed the risk of childhood and adolescent mental disorders following assisted reproduction. The study included 524 children born after IVF or ICSI and 22,009 children born after spontaneous conception. In an analysis adjusted for potential confounders, compared with spontaneously conceived children, there were no statistically significant increases in mental disabilities, disorders of psychological development (eg, autism spectrum disorders, speech and language disorders, others), attention-deficit/hyperactivity disorder or conduct, emotional, or social disorders.

Summary of Evidence
For individuals who have infertility who receive IVF with assisted hatching, the evidence includes RCTs, a systematic review, and retrospective studies. Relevant outcomes are health status measures and treatment-related morbidity. RCTs have not shown that assisted hatching improves the live birth rate compared with
standard care. Clinical pregnancy rates after assisted hatching have been mixed, but RCTs have generally not found improvements in assisted hatching vs standard care. A large observational study found that assisted hatching was associated with worse outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have infertility who receive IVF with embryo co-culture, the evidence includes RCTs and case series. Relevant outcomes are health status measures and treatment-related morbidity. Most clinical trials have not found improved implantation or pregnancy rates after co-culture, and studies have not reported live birth rates. Moreover, co-culture techniques have not been standardized. One RCT did report a higher clinical pregnancy rate with co-culture than with a standard practice control group, however, the process was novel and not yet fully evaluated. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who will undergo treatment that may lead to infertility who receive cryopreservation of ovarian tissue, the evidence includes case series that have reported on the technique as well as pregnancy and live birth rates after transplantation. Relevant outcomes are health status measures and treatment-related morbidity. The technique used has not been standardized, and there is a lack of controlled studies on health outcomes following cryopreservation of ovarian tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who will undergo treatment that may lead to infertility who receive cryopreservation of oocytes, the evidence includes RCTs and a systematic review assessing the technique in related populations. Relevant outcomes are health status measures and treatment-related morbidity. The systematic review found that fertilization rates ranged from 71% to 79%, and the clinical pregnancy rates per transfer ranged from 36% to 61%. The available studies have been conducted in highly select populations and may not be generalizable to the population of interest, women with cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have infertility who receive IVF with blastocyst transfer, the evidence includes RCTs and meta-analyses. Relevant outcomes are health status measures and treatment-related morbidity. The RCTs and meta-analyses have found that blastocyst transfer is associated with higher live birth rates than cleavage-stage transfer. One retrospective cohort study has reported a significantly higher rate of preterm birth after blastocyst-stage vs cleavage-stage transfer and did not find increased risks of other outcomes such as low birth rate or perinatal mortality. A retrospective registry review of a similar population reported different findings. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have male factor infertility who receive IVF with ICSI, the evidence includes observational studies and a systematic review. Relevant
outcomes are health status measures and treatment-related morbidity. No RCTs are available. Observational studies, which are subject to design limitations (eg, selection bias), have found similar rates of clinical pregnancy and live birth after ICSI and standard IVF, and a meta-analysis of observational studies found a higher rate of genitourinary malformations in children born after ICSI (but only when lower quality studies were included in the analysis). Multiple RCTs are needed to compare health outcomes after ICSI for male factor infertility and standard IVF. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have azoospermia who receive cryopreservation of testicular tissue as part of ICSI, the evidence includes no clinical trials. Relevant outcomes are health status measures and treatment-related morbidity. While cryopreservation of testicular tissue in adult men with azoospermia is a well-established component of the ICSI procedure, there is a lack of clinical trials assessing safety and efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are prepubertal boys with cancer who receive cryopreservation of testicular tissue, the evidence includes no clinical trials. Relevant outcomes are health status measures and treatment-related morbidity. No clinical trials were identified evaluating the safety and efficacy of cryopreservation of testicular tissue in prepubertal boys undergoing cancer therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 physician specialty societies and 2 academic medical centers while this policy was under review in 2012. There was general agreement that intracytoplasmic sperm injection and cryopreservation of testicular tissue in adult men with azoospermia as part of an intracytoplasmic sperm injection procedure may be considered medically necessary. Three of 5 reviewers who responded agreed that co-culture of embryos is considered investigational. In addition, 4 of 5 reviewers did not agree that blastocyst transfer is investigational; these reviewers considered blastocyst transfer to be medically necessary to decrease multiple gestations. Three of 6 reviewers agreed that cryopreservation of ovarian tissue or oocytes is investigational. The other three thought that cryopreservation of oocytes, but not ovarian tissue, is medically necessary. Clinical input on other policy statements was more variable.
Practice Guidelines and Position Statements

American Society for Reproductive Medicine and Society for Assisted Reproductive Technology
The American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) (2014) published joint guidelines on assisted hatching and in vitro fertilization (IVF). The single recommendation in these guidelines stated that assisted hatching should not be used routinely for all patients undergoing IVF.

In 2013, ASRM and SART published joint guidelines on mature oocyte cryopreservation. The guidelines stated: “evidence indicates that oocyte vitrification and warming should no longer be considered experimental” and included the following recommendations:

- “In patients facing infertility due to chemotherapy or other gonadotoxic therapies, oocyte cryopreservation is recommended with appropriate counseling.”
- “More widespread clinic-specific data on the safety and efficacy of oocyte cryopreservation in donor populations are needed before universal donor oocyte banking can be recommended.”
- “There are not yet sufficient data to recommend oocyte cryopreservation for the sole purpose of circumventing reproductive aging in healthy women.”
- “More data are needed before this technology should be used routinely in lieu of embryo cryopreservation.”

A 2012 committee opinion from ASRM and SART stated that intracytoplasmic sperm injection (ICSI) is a safe and effective treatment for male factor infertility. The opinion also indicated that ICSI for unexplained fertility, low oocyte yield, and advanced maternal age does not improve clinical outcomes. The opinion included a statement that ICSI may benefit patients undergoing IVF with preimplantation genetic testing, in vitro matured oocytes, and cryopreserved oocytes.

ASRM and SART also issued a committee opinion on blastocyst transfer in 2008, which was updated in 2013. The opinion concluded that “evidence supports blastocyst transfer in ‘good prognosis’ patients.”

American College of Obstetricians and Gynecologists
The American College of Obstetricians and Gynecologists (2014) endorsed the 2013 ASRM-SART joint guidelines on mature oocyte cryopreservation. The endorsement was affirmed in 2016.

American Society of Clinical Oncology
The American Society of Clinical Oncology (2018) updated its 2013 guidelines (with no changes to its recommendations) on fertility preservation for patients with cancer. The guidelines included the following recommendations for males and females, respectively.
“Recommendation 2.1. Sperm cryopreservation: Sperm cryopreservation is effective, and health care providers should discuss sperm banking with postpubertal males receiving cancer treatment.

Recommendation 2.2. Hormonal gonadoprotection: Hormonal therapy in men is not successful in preserving fertility. It is not recommended.

Recommendation 2.3. Other methods to preserve male fertility: Other methods, such as testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols."

“Recommendation 3.1. Embryo cryopreservation: Embryo cryopreservation is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization.

Recommendation 3.2. Cryopreservation of unfertilized oocytes: Cryopreservation of unfertilized oocytes is an option, particularly for patients who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing.

Agency for Healthcare Research and Quality
Myers et al (2008), in an evidence report conducted for the Agency for Healthcare Research and Quality, evaluated the effectiveness of assisted reproductive technology. They reviewed evidence on the outcomes of interventions used in ovulation induction, superovulation, and IVF for the treatment of infertility. Reviewers concluded that:

“[i]nterventions for which there was sufficient evidence to demonstrate improved pregnancy or live birth rates included: ..., a pertinent to this evidence review: (c) ultrasound-guided embryo transfer, and transfer on day 5 post-fertilization, in couples with a good prognosis; and (d) assisted hatching in couples with previous IVF failure. There was insufficient evidence on other interventions.

Infertility itself is associated with most of the adverse longer-term outcomes.”

Reviewers concluded that "[d]espite the large emotional and economic burden resulting from infertility, there was relatively little high-quality evidence to support the choice of specific interventions.” This conclusion was based primarily on studies that had pregnancy rates as the primary end point, not live births. In addition, studies used multiple assisted hatching techniques.

U.S. Preventive Services Task Force Recommendations
Not applicable.
Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
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<tbody>
<tr>
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<td><strong>Ovarian tissue cryopreservation</strong></td>
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<td>NCT02646384</td>
<td>Ovarian Tissue Freezing For Fertility Preservation In Girls Facing A Fertility Threatening Medical Diagnosis Or Treatment Regimen: A Study By The National Physicians Cooperative of the Oncofertility Consortium At Northwestern University</td>
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<td>Validation of a Method to Search Residual Disease in Auto-cryopreserved Ovarian Tissues</td>
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<td>NCT02846064</td>
<td>Development of Ovarian Tissue Autograft in Order to Restore Ovarian Function</td>
<td>50</td>
<td>Oct 2020</td>
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<tr>
<td>NCT02678910</td>
<td>Ovarian Tissue Freezing For Fertility Preservation In Women Facing A Fertility Threatening Medical Diagnosis/Treatment</td>
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<tr>
<td>NCT01993732</td>
<td>Ovarian Tissue Cryopreservation in Females Undergoing Procedures That Will Potentially Lead To Loss of Ovarian Function</td>
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<td>Dec 2041</td>
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<td><strong>Blastocyst transfer</strong></td>
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<td>NCT02148393</td>
<td>Implantation Enhancement by Elective Cryopreservation of All Viable Embryos</td>
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<td>NCT02999958*</td>
<td>Adding Antioxidants Into Human Sequential Culture Media System</td>
<td>128</td>
<td>Mar 2018</td>
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<td>NCT02746562</td>
<td>A Multicentre Randomized Controlled Trial of a &quot;Freeze-All and Transfer Later&quot; Versus a Conventional &quot;Fresh Embryo Transfer&quot; Strategy for Assisted Reproductive Technology (ART) in Women With a Regular Menstrual Cycle</td>
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<td>NCT03173885</td>
<td>An RCT Evaluating the Implantation Potential of Vitrified Embryos Screened by Next Generation Sequencing Following Trophoderm Biopsy, Versus Vitrified Unscreened Embryos in Good Prognosis Patients Undergoing IVF</td>
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<td><strong>Testicular tissue cryopreservation</strong></td>
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<td>NCT02872532</td>
<td>Testicular Tissue Cryopreservation for Fertility Preservation in Males Facing Fertility Threatening Diagnoses or Treatment Regimens</td>
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<td>NCT02972801</td>
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<td>Jan 2021</td>
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</table>

NCT: national clinical trial.
\* Denotes industry-sponsored or cosponsored trial.
References


Billing Coding/Physician Documentation Information
(See Tables Above)

The following CPT codes describe procedures that would be routinely performed in all ART procedures involving in vitro fertilization (IVF):

- **58970**: Oocyte retrieval
- Either:
  - **89250**: Culture and fertilization of oocyte, less than 4 days; **OR**
  - **89272**: Culture and fertilization of oocyte, greater than 4 days.
- Either
  - **89268**: Insemination of oocytes; **OR**
  - **89280 / 89281**: Assisted oocyte fertilization, microtechnique, less than or greater than 10 oocytes, respectively
- **89260 or 89261**: Sperm isolation, simple or complex
- **89255**: Preparation of embryo for transfer
- **58974** or **58976**: Embryo, zygote, or gamete transfer, intrauterine or intrafallopian

The following CPT codes describe procedures that would not be routinely performed in all ART procedures involving IVF.

- **89257**: Sperm identification from aspiration. Only performed in patients with oligospermia who have undergone a prior testicular or epididymal aspiration; typically performed as a part of an intracytoplasmic sperm injection procedure (ICSI).
- **89264**: Sperm identification from biopsied testis tissue. Only performed in patients with oligospermia who have undergone a prior testicular biopsy; typically performed as a part of an ICSI procedure.
- **89253**: Assisted hatching. Only performed in women over the age of 40, or in cases in which prior ART attempts resulted in failed implantation.
- **89256**: Preparation of cryopreserved embryos
- **89258**: Cryopreservation of embryos
- **89259**: Cryopreservation of sperm
- **89342-89356**: Code range, cryopreservation and thawing of various components

The following CPT codes describe procedures that would be routinely performed as part of an intrauterine or intracervical artificial insemination:

- **58321**: Artificial insemination; intracervical
- **58322**: Artificial insemination; intrauterine
- **58323**: Sperm washing for artificial insemination

Note also that other “S” codes are available (see Coding section, above) that describes in vitro fertilization globally.

- **S4013**: Complete cycle, gamete intrafallopian transfer (GIFT), case rate
- **S4014**: Complete cycle, zygote intrafallopian transfer (ZIFT), case rate
- **S4017**: Incomplete cycle, treatment cancelled prior to stimulation, case rate
- **S4018**: Frozen embryo transfer procedure cancelled before transfer, case rate
- **S4042**: Management of ovulation induction (interpretation of diagnostic tests and studies, non-face-to-face medical management of the patient), per cycle

**ICD-10 Codes.**

- N46.01: Male infertility, code range
- N46.9
- N73.6: Female pelvic peritoneal adhesions
- N80.1: Endometriosis code range
- N80.9
- N97.1: Female infertility, code range
- N97.9
- N99.4: Postprocedural pelvic peritoneal adhesions
### Additional Policy Key Words
N/A

### Policy Implementation/Update Information

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<td>12/1/18</td>
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