KAISER PERMANENTE® **Northwest Region Utilization Review**

UR 68: Assisted Reproductive Technology (ART) Medical Necessity Criteria

Department: Non-Behavioral Health	Number: UR 68
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ASSISTED REPRODUCTIVE TECHNOLOGY MEDICAL NECESSITY CRITERIA

DEFINITIONS

ART- Assisted Reproductive Technology refers to procedures in which pregnancy is attempted through the manipulation of sperm and egg outside the body, such as in vitro fertilization (IVF) or gamete intra-fallopian transfer (GIFT).

IVF- In-vitro fertilization involves retrieving an egg from the woman, combining with sperm in a lab, observing and raising the embryos in the lab for 3 to 5 days, then transferring the resulting embryo back into her uterus.

GIFT- gamete intra-fallopian transfer is a modified version of in vitro fertilization (IVF). GIFT involves retrieving an egg from the woman, combining with sperm in a lab then immediately transferring the unfertilized egg and sperm into her fallopian tube with fertilization taking place in the fallopian tube instead of in a laboratory dish.

ZIFT- zygote intra-fallopian transfer is a modified version of in vitro fertilization (IVF). ZIFT involves retrieving an egg from the woman, combining with sperm in a lab then transferring the fertilized egg (called a zygote) into her fallopian tube before cell division takes place. The zygote is transferred the next day after fertilization occurs.

IUI- Intra-uterine insemination is the placement of washed and concentrated sperm via a catheter into a woman's uterus when she is ovulating. It is often combined with superovulation medicine to increase the number of available eggs, which can result in multiple gestation.

POLICY AND CRITERIA

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of a NCD or LCD, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "Assisted Reproductive Technology" for medical necessity determinations for Medicare members.

Assisted reproductive technology may be indicated when A-C below are present:

A. Individual 45 years or younger with use of autologous oocytes and 1, 2 and 3 below.

1. Infertility, as defined by **1 or more** of the following:
   a) Failure to conceive after regular unprotected sexual intercourse for 1 year or more for female 34 years or younger
   b) Failure to conceive after regular unprotected sexual intercourse for 6 months or more for female 35 years old or older.
   c) Individual or partner with infertility due to medical or surgical treatment (e.g., chemotherapy, radiotherapy, gonadotoxic medication, oophorectomy, orchiectomy)
   d) Individual with impending infertility due to planned cancer treatment for cure (eg, chemotherapy or oophorectomy)
   e) Partner is HIV positive and **ALL** of the following:
      i. Adherent with highly active antiretroviral therapy
      ii. Washed sperm needed for insemination to prevent HIV transmission
   f) Male partner with infertility due to cancer therapy (eg, orchiectomy or chemotherapy)
   g) Individual with nonobstructive azoospermia or severe oligospermia
   h) Partner with paraplegia, and sperm retrieval needed to achieve pregnancy (eg, electro-ejaculation or surgical sperm retrieval)
   i) Prior failed cycle of in vitro fertilization or intracytoplasmic sperm injection

2. Infertility evaluation and treatment performed, as indicated by **1 or more** of the following:
   a) Individual with impending infertility due to planned cancer treatment for cure (eg, chemotherapy or oophorectomy)
   b) Individual with infertility due to medical or surgical treatment (e.g., chemotherapy, radiotherapy, gonadotoxic medication, oophorectomy) and **ALL** of the following:
      i. No evidence of tumor recurrence, as indicated by **1 or more** of the following:
         - Two years or more after completion of cancer treatment for gynecologic tumors
         - Two years or more after completion of hematopoietic stem cell transplant
         - Three years or more after initial diagnosis in individual with breast cancer without axillary lymph node involvement
         - Five years or more after initial diagnosis in individual with breast cancer with axillary lymph node involvement
         - After completion of adjuvant tamoxifen, if appropriate, for breast cancer
      ii. Patient had embryo or oocyte cryopreservation prior to treatment.
   c) Hysterosalpingogram shows absent or nonpatent fallopian tube (eg, from prior ectopic pregnancy or pelvic inflammatory disease)
   d) In vitro fertilization or intracytoplasmic sperm injection needed, as indicated by **1 or more** of the following:
      i. Cryopreserved sperm needed from partner (eg, after chemotherapy)
      ii. Prior in vitro fertilization or intracytoplasmic sperm injection cycle resulted in failed fertilization or pregnancy
      iii. Surgical sperm retrieval needed for azoospermia or severe oligospermia in male partner

e) Treatment for infertility, including specific disorders, as indicated by **1 or more** of the following:
   i. Anovulatory female without polycystic ovary syndrome or other endocrinopathy and **1 or more** of the following:
      - For female 34 years or younger: trial of at least 4 cycles of clomiphene citrate or letrozole and intrauterine insemination
      - For female 35 to 37 years of age: trial of at least 3 cycles of clomiphene citrate or letrozole and intrauterine insemination
      - For female 38 years or older: proceed with in vitro fertilization immediately, without prior intrauterine insemination.
   ii. Endocrinopathy in female (eg, hypothyroidism, adrenal disorders, pituitary tumor)
   iii. Endometriosis
   iv. Failure of 12 cycles of donor intrauterine insemination
   v. Hypogonadotrophic hypogonadism in male partner
   vi. Intrauterine pathology (eg, adhesions, polyps)
   vii. Pelvic adhesions
   viii. Polycystic ovary syndrome, treated with **ALL** of the following:
      - Other causes of infertility ruled out or treated (eg, thyroid disease, hyperprolactinemia, male factor infertility)
      - Treated with at least 6 cycles of clomiphene citrate or letrozole
   ix. Repair of varicocele
   x. Retrograde ejaculation treated with pharmacotherapy
   xi. Submucosal leiomyomas
   xii. Tubal anastomosis (ie, reversal of tubal ligation)

f) Unexplained infertility and **ALL** of the following:
   i. Conventional treatment of unexplained infertility has failed, as indicated by **1 or more** of the following:
      - For female 34 years or younger: trial of at least 4 cycles of controlled ovarian stimulation (eg, clomiphene citrate or letrozole) and intrauterine insemination
      - For female 35 to 37 years of age: trial of at least 3 cycles of controlled ovarian stimulation (eg, clomiphene citrate or letrozole) and intrauterine insemination
      - For female 38 years or older: proceed with in vitro fertilization immediately, without prior intrauterine insemination.
   ii. Normal female serum levels of **ALL** of the following:
      - Estradiol
      - FSH
      - Progesterone (in midluteal phase)
      - Prolactin
      - TSH
   iii. Normal hysterosalpingogram and sonohysterography
   iv. Normal sperm count, motility, and morphology

3. **1 or more** of the following:
   a) Embryo or egg cryopreservation needed for impending infertility due to planned cancer treatment

b) Maximum number of embryos to be transferred is consistent with current evidence to limit risk of multiple-birth pregnancies, as indicated by **1 or more** of the following:
   i. One fresh or frozen single-embryo transfer for individual 36 years or younger during first 3 in vitro fertilization cycles
   ii. Up to 2 fresh or frozen embryos transferred for individual 36 years or younger after first 3 failed single-embryo transfer in vitro fertilization cycles
   iii. One fresh or frozen single-embryo transfer for individual 37 years of age during first in vitro fertilization cycle
   iv. Up to 2 fresh or frozen embryos transferred for individual37 years of age after first failed in vitro fertilization cycle
   v. Up to 2 fresh or frozen embryos transferred for individual 38 years of age if prognosis is favorable and/or additional embryos are available for cryopreservation
   vi. Up to 3 fresh or frozen embryos transferred for individual 38 years of age if prognosis is unfavorable and no additional embryos are available for cryopreservation
   vii. Up to 3 fresh or frozen embryos transferred for individual 39 to 40 years of age if prognosis is favorable and/or additional embryos are available for cryopreservation
   viii. Up to 4 fresh or frozen embryos transferred for individual 39 to 40 years of age if prognosis is unfavorable and no additional embryos are available for cryopreservation
   ix. Up to 5 fresh or frozen embryos transferred for individual 41 to 45 years of age

B. No hydrosalpinx or after treatment with tubal occlusion or salpingectomy
C. No prior in vitro fertilization cycle, or maximum number of prior in vitro fertilization cycles has not exceeded a total of 6 cycles without a live birth

SPECIAL GROUP CONSIDERATIONS

ART may be excluded from coverage. Check CM for exclusions or limitations.

OR PEBB- Check infertility benefit with each request as to whether females must be diagnosed as *infertile* to qualify for infertility treatment.

Cryopreservation is typically excluded from coverage unless the member has coverage for ART, in which case, the associated cryopreservation is also covered. The Exclusion is applied when cryopreservation is requested/billed as a distinct procedure aside from a covered ART procedure.
When cryopreservation is covered, procedures to obtain eggs/sperm are also covered.

RATIONALE

EVIDENCE BASIS

MCG reviewed the evidence on assisted reproductive technology (ART) in 2022. Their findings are provided below:

For infertility, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. Guidelines recommend mature oocyte, embryo, or sperm cryopreservation prior to planned chemotherapy.[1-4] Multiple-embryo

transfer is associated with an increased risk for multiple-gestation pregnancies and pregnancy complications, including cesarean birth, preeclampsia, premature delivery, and low-birth-weight infants.[5, 6] Additionally, analysis of a US database found a significant adverse effect on intrauterine growth for live singleton and twin births resulting from transfer of multiple embryos.[7] Guidelines on the number of embryos to transfer have been developed by professional societies in order to optimize healthy live births and minimize multiple-gestation pregnancies.[8-10] Assisted reproductive technology registries from 36 European countries for 2008 show an overall distribution of the transfer of 1, 2, 3, and 4 or more embryos as 22.4%, 53.2%, 22.3%, and 2.1%, respectively, resulting in proportions of singleton, twin, and triplet deliveries of 78.3%, 20.7%, and 1.0%, respectively.[11] A systematic review and meta-analysis of randomized controlled trials concluded that increasing the number of single-embryo transfer attempts to 3 cycles using fresh or frozen embryos in women younger than 36 years results in a cumulative live birth rate similar to double-embryo transfer and reduces the likelihood of multiple births by 94%.[12] A meta-analysis of individual patient data from randomized trials reported that elective single-embryo transfer resulted in a lower pregnancy rate than double-embryo transfer in a fresh in vitro fertilization cycle; however, the difference was almost completely overcome by an additional frozen single-embryo transfer cycle. Additionally, the rate of multiple-gestation pregnancy and risk of preterm birth and delivery of a low-birth-weight infant were decreased with single-embryo transfer.[13] A systematic review and meta-analysis reported that elective single-embryo transfer is associated with decreased risk of preterm birth and low birth weight as compared with double-embryo transfer, but with higher risk of preterm birth as compared with spontaneously conceived singleton infants.[14] A multicenter randomized controlled trial of 1650 women with infertility found that frozen single blastocyst transfer was associated with an improved singleton live birth rate compared with fresh single blastocyst transfer (50% vs 40%, respectively). However, frozen single blastocyst transfer was also associated with a higher risk of preeclampsia (3.1% vs 1.0%, respectively) which the authors advise warrants additional evaluation.[15] A national registry study of the outcomes by number of embryos transferred (124,148 IVF cycles, 32,732 cycles with complete outcomes data available) reported that the odds of live birth were similar regardless of whether 1, 2, or 3 embryos were transferred; however, all adverse perinatal outcomes (multiple births, prematurity, small for gestational age) occurred more frequently when 3 or more embryos were transferred. The odds of live birth were higher with double-embryo transfer in all age groups; however, the association was stronger in women older than 40 years. Multiple birth risk increased with double-embryo transfer in all age groups, but was substantially lower in women age 40 years and older. The authors concluded that the findings supported restricting embryo transfer to fewer than 3.[16] A practice guideline recommends that women age 35 to 40 years be considered for elective single-embryo transfer if they have top-quality blastocyst-stage embryos available for transfer.[17] For women age 40 to 42 years, another practice guideline recommends double-embryo transfer.[2]

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