

# Pharmacy Focus: Infertility Programs and High-Cost Newborns



## Overview

High-cost claims related to premature births, high-risk pregnancies and congenital malformations continue to dominate annual large claim reports. Year-over-year comparisons from the National Center for Health Statistics indicate the total number of U.S. births continues to decline, while the preterm birth rate is up for the fifth year in a row. They also report that there is a decrease in the number of births for females aged 15 to 34 years, while there is an increase for females 35 to 44 years.

This data raises some concern, as preterm births are associated with several neonatal medical conditions, including heart defects, undeveloped organs and malformations. Understanding more about potential causes of preterm births may help to reduce them – and the acute stress they bring to families – as well as addressing other delayed concerns, such as childhood cancers. Preterm births and significant complications often are the result of a high-risk pregnancy, so it's important to look at factors that are tied to complex pregnancies and resultant trends. Risks associated with infertility management also have been attributed to preterm births and significant complications. As a result, they are reviewed together in this article.

## Factors of a High-Risk Pregnancy

There are a number of factors/conditions that can contribute to a high-risk pregnancy.

**The following considers the most commonly seen:**

### Existing Health Conditions

- High blood pressure
- Polycystic Ovary Syndrome (PCOS)
- Diabetes
- Kidney disease
- Autoimmune disease
- Thyroid disease
- Obesity
- HIV/AIDS

### Maternal Age

#### Young age (generally <20 years old):

- Anomalous pulmonary venous return
- Amniotic band sequence
- Gastroschisis

#### Advanced age (generally >40 years old):

- Cardiac defects
  - Ventricular septal defects
  - Atrial septal defects
  - Tetralogy of Fallot
- Esophageal atresia
- Hypospadias
- Craniosynostosis

### Advanced Paternal Age (generally >40 years old):

- Increased risk of childhood cancer
  - Leukemia
  - Non-Hodgkin's lymphoma
  - Pediatric central nervous system tumors
  - Breast cancer
- Increased risk of birth defects
  - Cleft lip
  - Diaphragmatic hernia
  - Right ventricular outflow tract obstruction
  - Pulmonary stenosis
- Evidence that females born to fathers of advanced age have an increased risk of spontaneous germline mutations in X-linked disease:
  - Hemophilia A and B
  - Duchenne muscular dystrophy
  - Hunter syndrome
  - Lesch-Nyhan disease

*Continued...*

## Impacts of Assisted Reproductive Technology, Infertility Treatments and High-Risk Pregnancies

Correlation has been made between assisted reproductive technology (ART), fertility medications and high-risk pregnancies to devastating medical conditions that last a lifetime. Consideration of the true cost of not covering the therapies but covering the delivery and the new dependent is important.

ART, with in vitro fertilization (IVF) being the most common, is often an option to treat infertility in couples struggling to conceive. It is usually reserved until after failure of less invasive therapies, including the management of the underlying cause. Over the past decade, ART use has almost doubled. According to the Centers for Disease Control and Prevention (CDC), approximately 1.9% or 81,478, of the infants born in the United States every year are conceived using ART.

This raises some concern, as ART, preterm births and multiple gestations have been associated with several high-risk medical conditions such as heart defects and even cancer. It is important to address these risks and consider administrator-guided programs that engage high quality providers experienced in the appropriate and effective use of ART.

### Risks of ART Therapy

#### Multiple Gestations

- Preterm birth and its consequences:
  - Cerebral palsy
  - Retinopathy
  - Bronchopulmonary dysplasia
- Fetal growth restriction and its consequences:
  - Polycythemia
  - Hypoglycemia
  - Necrotizing enterocolitis

#### Maternal Complications

- Preeclampsia (ICD-10 Code: O14)
- Gestational diabetes (ICD-10 Code: O24.419)
- Placenta previa: (ICD-10 Code: O44.10)
- Placental abruption (ICD-10 Code: O45)
- Cesarean delivery (ICD-10 Code: O82 series)

#### Birth Defects

- Atrial septal heart defects
- Cleft lip
- Esophageal atresia
- Anorectal atresia
- Angelman Syndrome
  - A rare genetic and neurological disorder
  - May include severe developmental delay, tremulousness with jerky movements, microcephaly, distinct behavioral pattern characterized by a happy disposition, seizures, scoliosis and feeding difficulties
  - Advances in gene therapy techniques have the potential for providing meaningful treatment and/or cure
- Beckwith-Wiedemann Syndrome (BWS)
  - Most common overgrowth and cancer predisposition disorder
  - Increased risk of developing certain childhood cancers, most commonly Wilms tumor and hepatoblastoma
  - May include above-average birth weight, increased growth after birth, enlargement of certain internal organs and abdominal wall defects
  - If a tumor develops, treatment methods may include surgery, use of certain chemotherapy, radiation therapy, etc.

Continued...

Infertility Treatment Options (include but are not limited to):

Common Medications	Dose	How It Works	Common Place in Therapy	Cost
<b>Clomiphene Citrate</b> (Clomid®)	Five consecutive days	<b>Females</b> – Ovulation induction (HIGH RISK: 5-8% chance of multiple gestation) <b>Males</b> – Increase testosterone	<ul style="list-style-type: none"> <li>• Early on; prior to ART or in conjunction with ART therapies</li> <li>• Maximum of six cycles</li> </ul>	<\$15,000 PPY
<b>Aromatase Inhibitors:</b> Letrozole (Femara®) Anastrozole (Arimidex®)	Five consecutive days	<b>Females</b> – Ovulation induction <b>Males</b> – Increase testosterone	<ul style="list-style-type: none"> <li>• Early on; prior to ART or in conjunction with ART therapies</li> </ul>	<\$15,000 PPY
<b>Metformin</b> (Glucophage®)	Daily	<b>Females</b> – Ovulation induction (when used for 4-6 months) <b>Males</b> – Increase sperm count	<ul style="list-style-type: none"> <li>• Early on; prior to ART or in conjunction with ART therapies</li> </ul>	<\$15,000 PPY
<b>Progesterone</b> (Endometrin®), (Crinone®)	Based on regimen	<b>Females</b> – Supports implantation	<ul style="list-style-type: none"> <li>• Early on; prior to ART or in conjunction with ART therapies</li> <li>• To prevent preterm delivery</li> </ul>	<\$15,000 PPY
<b>Gonadotropins:</b> Bravelle®, Repronex®, Gonal-F®, Follistim®	Based on regimen	<b>Females</b> – Ovulation induction (HIGH RISK: Up to a 30% risk for multiple gestations) <b>Males</b> – Increase testosterone	<ul style="list-style-type: none"> <li>• In conjunction with ART therapies</li> <li>• Maximum of six cycles</li> </ul>	<\$15,000 per treatment
<b>Human chorionic gonadotropin (hCG):</b> Profasi®, Ovidrel®, Novarel®, Pregnyl®	Based on regimen	<b>Females</b> – Ovulation induction <b>Males</b> – Increase testosterone	<ul style="list-style-type: none"> <li>• In conjunction with ART therapies</li> </ul>	<\$15,000 per treatment
<b>Human menopausal gonadotropin Menotropins</b> (Menopur®)	Based on regimen	<b>Females</b> – Ovulation induction <b>Males</b> – Treatment of hypogonadism	<ul style="list-style-type: none"> <li>• Maximum of 6-12 cycles</li> <li>• In conjunction with ART therapies</li> <li>• In conjunction with Bravelle®</li> </ul>	<\$15,000 per treatment
<b>GnRH antagonists:</b> Cetrotide®, Antagon®	Based on regimen	<b>Females</b> – Ovulation stimulation <b>Males</b> – No human use identified	<ul style="list-style-type: none"> <li>• In conjunction with ART therapies</li> <li>• In conjunction with hCG and gonadotropins</li> </ul>	<\$15,000 per treatment

Continued...

## HMConnects™ Observations & Recommendations

Our HMConnects™ cost containment program recognizes the need to identify preterm births. As shared in our Five-Year Claims History report, HM Insurance Group has consistently seen neonatal as a top diagnosis category for first-dollar claims exceeding \$1 million. In fact, internal claims reports have shown that ongoing management in NICUs has led to a current mean client cost in excess of \$2,500,000 for such cases.

For clients working to better contain costs, evaluating the applicable terms, conditions, limitations and exclusions in the plan document and exploring Reproductive Centers of Excellence Programs could help to:

- Increase the number of births carried closer to term
- Decrease the number of multiple births
- Provide higher quality services during the perinatal period, including:
  - Low-dose protocols
  - Close monitoring
  - Use of strategies to promote singleton pregnancies
  - Requirement of prescription versions of prenatal vitamins with folate

Clients may want to consider evaluating the terms of the plan document to specify whether coverage is limited to:

- Baseline cost around \$12,000 for IVF +/- ICSI
- Baseline cost around \$25,000 for donors
- Baseline cost around \$50,000 for gestational carriers

**Note:** Medical incidents can occur with traditionally conceived pregnancies/newborns as well and may not occur with those achieved through fertility support. This document is sharing information about trends that have been seen with some newborns conceived through infertility programs.

**Pharmacy Focus** provides valuable information about pharmaceutical industry developments and their associated costs that can impact the growing claims trend in the self-funded insurance market. Be aware of influences and gain insight into approaches that may help to contain costs. Please share topic suggestions or feedback with [HMPHarmacyServices@hmg.com](mailto:HMPHarmacyServices@hmg.com).



Products are underwritten by HM Life Insurance Company, Pittsburgh, PA, Highmark Casualty Insurance Company, Pittsburgh, PA, or HM Life Insurance Company of New York, New York, NY.

This is an informational document only and is not intended to provide legal advice, tax advice or advice on your health plan's content and design. This document is not meant to address federal or other applicable laws for health plans. This document only includes HM's suggested best practices for certain provisions in a health plan. You should consult with your legal counsel and/or a qualified plan design professional.

**References:** "Births: Final Data for 2019," national Vital Statistics Reports, March 23, 2021, <https://www.cdc.gov/nchs/data/nvsr/nvsr70/nvsr70-02-508.pdf>, accessed June 14, 2021; "Births and Natality," National Center for Health Statistics, <https://www.cdc.gov/nchs/fastats/births.htm>, accessed June 11, 2021; "What Are Some Factors That Make a Pregnancy High Risk?" National Institutes of Health, <https://www.nichd.nih.gov/health/topics/high-risk/conditioninfo/factors>, date accessed 06-08-21; "Advanced Paternal Age, Infertility, and Reproductive Risks: A Review of the Literature," Justin S. Brandt, Mayra A Cruz Ithier, Tod Rosen, Alena Ashkinadze, December 5, 2018, <https://pubmed.ncbi.nlm.nih.gov/30520056/>, accessed June 11, 2021; Association Between Maternal Age and Birth Defects of Unknown Etiology – United States, 1997-2007, Gill, S. K., Broussard, C., Devine, O., Green, R. F., Rasmussen, S. A., Reefhuis, J. and The National Birth Defects Prevention Study, July 21, 2012, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4532312/>, accessed June 11, 2021; "ART Success Rates," Centers for Disease Control and Prevention, <https://www.cdc.gov/art/artdata/index.html>, accessed June 10, 2021; "Assisted Reproductive Technology and Major Structural Birth Defects in the United States," J Reefhuis, M A Honein, L A Schieve, A Correa, C A Hobbs, S A Rasmussen, National Birth Defects Prevention Study, <https://pubmed.ncbi.nlm.nih.gov/19010807/>, accessed June 8, 2021; "Infertility, Assisted Reproductive Technology, and Adverse Pregnancy Outcomes: Executive Summary of a National Institute of Child Health and Human Development Workshop," Uma M Reddy, Ronald J Wapner, Robert W Rebar, Richard J Tasca, <https://pubmed.ncbi.nlm.nih.gov/17400861/>, accessed June 8, 2021; "Perinatal Risks Associated with Assisted Reproductive Technology," Committee Opinion, The American College of Obstetricians and Gynecologists, <https://www.acog.org/-/media/project/acogorg/clinical/files/committee-opinion/articles/2016/09/perinatal-risks-associated-with-assisted-reproductive-technology.pdf>, accessed June 8, 2021; "Multiple Gestation Associated with Infertility Therapy," an American Society for Reproductive Medicine Practice Committee Opinion, [https://www.asrm.org/globalassets/asrm-content/news-and-publications/practice-guidelines/for-non-members/multiple\\_gestation\\_associated\\_with\\_infertility\\_therapy.pdf](https://www.asrm.org/globalassets/asrm-content/news-and-publications/practice-guidelines/for-non-members/multiple_gestation_associated_with_infertility_therapy.pdf), accessed June 11, 2021; "Angelman Syndrome," National Organization for Rare Disorders, <https://rarediseases.org/rare-diseases/angelman-syndrome/>, accessed June 11, 2021; "Beckwith-Wiedemann Syndrome," National Organization for Rare Disorders, <https://rarediseases.org/rare-diseases/beckwith-wiedemann-syndrome/>, accessed June 11, 2021; "Medications for Inducing Ovulation," American Society for Reproductive Medicine, [https://www.reproductivefacts.org/globalassets/rf/news-and-publications/bookletsfact-sheets/english-fact-sheets-and-info-booklets/booklet\\_medications\\_for\\_inducing\\_ovulation.pdf](https://www.reproductivefacts.org/globalassets/rf/news-and-publications/bookletsfact-sheets/english-fact-sheets-and-info-booklets/booklet_medications_for_inducing_ovulation.pdf), accessed June 8, 2021; "Metformin Therapy for the management of Infertility in Women with Polycystic Ovary Syndrome," BJOG: An International Journal of Obstetrics and Gynaecology, <https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.14764>, accessed June 11, 2021; "ART Medications," Society for Assisted Reproductive Technology, <https://www.sart.org/patients/a-patients-guide-to-assisted-reproductive-technology/general-information/art-medications/>, accessed June 8, 2021; "Male Fertility Drugs," University of Utah, <https://healthcare.utah.edu/fertility/treatments/male-fertility-drugs.php>, accessed June 15, 2021; "CLOMID™," Prescribing Information, Food and Drug Administration, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/016131s026lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/016131s026lbl.pdf), accessed June 15, 2021; "Centrotide™," Prescribing Information, Food and Drug Administration, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2000/211971bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/211971bl.pdf), accessed June 15, 2021; "Antagon," Prescribing Information, Food and Drug Administration, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/1999/210571bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/210571bl.pdf), accessed June 15, 2021; "Endometrin™ (Progesterone)," Prescribing Information Food and Drug Administration, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/022057s001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022057s001bl.pdf), accessed June 15, 2021; "Crinone® (Progesterone Gel)," Prescribing Information, Food and Drug Administration, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/020701s026lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020701s026lbl.pdf), accessed June 15, 2021; "Femara (Letrozole)," Prescribing Information, Food and Drug Administration, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/020726s0271bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020726s0271bl.pdf), accessed June 15, 2021; "Pregnyl®," Prescribing Information, Food and Drug Administration, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/017692s021bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/017692s021bl.pdf), accessed June 15, 2021; "Bravelle®," Prescribing Information, Food and Drug Administration, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/021289s019bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021289s019bl.pdf), accessed June 15, 2021; "Menopur™," Prescribing Information, Food and Drug Administration, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/021663s014bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021663s014bl.pdf), accessed June 15, 2021; "Increased Success and Safety in Assisted Reproductive Technology By Using Elective Single Embryo Transfer," The American College of Obstetricians and Gynecologists, <https://www.acog.org/news/news-releases/2016/08/increased-success-and-safety-in-assisted-reproductive-technology-by-using-elective-single-embryo-transfer>, accessed June 8, 2021; "How Much Does IVF Really Cost," Rachel Gurevich, RN, Very Well Family, <https://www.verywellfamily.com/how-much-does-ivf-cost-1960212>, accessed June 22, 2021.