

Innovations in Assisted Reproductive Technologies For Women

Introduction to Infertility in Women Epidemiology and Causes

Infertility is a common condition that can be attributed to male or female reproductive health issues. One-third of the time, male factor infertility is the cause of infertility; one-third of the time, it is due to female factor infertility; and the remaining cases are due to either a combined or an unknown reason.¹ Infertility in men may be caused by disruption of testicular function, disruption of ejaculatory function, hormonal reasons or genetic disorders.² Infertility is defined as frequent contraceptive-free sexual intercourse each month and the inability to conceive within the last 12 months or longer.³ According to data from the National Health Statistics Report from 2015 to 2019, 10.43 million women aged 15 to 49 years have a fertility problem, and 2.45 million women who are married have infertility, accounting for 8.5% of married women in this age group.³ In the same report, 11.4% of men aged 15 to 49 years had some type of infertility.

There are a variety of common causes of infertility in women, such as hormonal imbalances, anatomical issues and lifestyle factors. Causes of infertility related to disruption of ovarian function include polycystic ovary syndrome (PCOS), which is the most common cause of infertility, diminished ovarian reserve and functional hypothalamic amenorrhea.² Infertility may also be caused by fallopian tube obstruction, such as in the case of history of pelvic infection with sexually transmitted infections, endometriosis or prior abdominal surgery.⁴ Uterine abnormalities resulting from conditions such as uterine fibroids may also play a role.² Additionally, lifestyle factors may contribute to infertility; these include nutrition status, weight, exercise, physical stress, psychological stress and medications, among others.⁴

Physical and Psychosocial Burden

The emotional and psychological effects that infertility may take on women are significant. A meta-analysis evaluating four studies reporting on the psychological impact of infertility supported a significant association between infertility and psychological distress, anxiety and depression in females (odds ratio [OR], 1.63; 95% CI, 1.24-2.13; $I^2 = 57\%$).⁵ Failure of one treatment for infertility is significantly associated with psychological symptoms such as anxiety, and patients who experience two treatment failures had higher rates of depression on a Hospital Anxiety and Depression Scale (HADS) compared with those who did not undergo

infertility treatment.⁶ These higher levels of depression may make some women less likely to initiate infertility treatment, as 35% of women with depression initiate infertility treatment compared with 64% of women without depression (p-value = 0.02).⁶

Stress may lead to increased infertility. In a study of women undergoing in vitro fertilization (IVF), higher levels of cortisol occurred more frequently in patients who were subsequently not pregnant on follow-up (mean [SD] hair cortisol level, 19.4 [4.8] pg/mL in patients subsequently pregnant compared with 24.9 [14.4] pg/mL in those subsequently not pregnant), suggesting that stress may negatively impact fertility outcomes.⁷ Women with the highest levels of the stress biomarker salivary alpha-amylase in the study had 29% decreased odds of pregnancy (fecundability adjusted OR, 0.71; 95% CI, 0.51-1.00).^{7,8}

Addressing infertility is important to help mitigate these physical and psychological burdens. Women with infertility frequently experience social and relationship challenges and commonly experience violence, divorce and social stigma.⁹ Addressing infertility management can help to mitigate gender inequality. Although men may also contribute to infertility, women are often perceived to be the cause.⁹ Women who experience infertility report stigma associated with infertility as well as psychological stress, depression, perceptions of negative responses from family or neighbors, criticism, exclusion and social isolation.¹⁰

Infertility Treatment

There are many ways to assist in the management of infertility. The type of treatment offered by health care providers depends on several factors, one of which is the cause of the infertility.

Treatments Without Assisted Reproductive Technology

During ovulation induction treatment, medications such as clomiphene citrate and letrozole can be given to stimulate ovulation. Medications that stimulate or regulate ovulation are the main treatment for cases in which women are infertile because of ovulation disorders. Ovulation induction medications result in increases in follicle stimulating hormone (FSH) and luteinizing hormone (LH) to subsequently stimulate ovulation.¹¹ Clomiphene citrate and letrozole are oral medications that are first-line treatment in women younger than 39 years of age who have PCOS.¹¹

During intrauterine induction (IUI), previously termed *artificial insemination*, sperm are inserted directly into the uterus.⁴ IUI is often recommended in cases in which the woman does not ovulate normally but can ovulate with medication.⁴ IUI may also be used in the case of unexplained infertility, mild male factor infertility and same-sex couples.⁴

Treatments Available in Assisted Reproductive Technology

Assisted reproductive technology (ART) is one of the management strategies in infertility treatment. ART includes fertility treatments during which eggs or embryos are handled ex vivo (outside the body).⁴ Eggs are removed from the ovaries using a needle and then are combined with the sperm to form embryos. The formed embryos may then be placed in a woman’s uterus, frozen for future use or donated to others.⁴ Types of ART further discussed below will include in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).

In IVF, mature eggs are collected from the ovaries and fertilized with a sperm sample. Then, at least one fertilized egg is placed into the uterus; this is known as embryo transfer (ET).¹² IVF may use a couple’s own eggs and sperm or those from donors.¹² Couples may attempt other procedures before IVF, such as fertility medication or intrauterine insemination to directly inject sperm into the uterus during ovulation.¹² IVF is the main treatment offered for women with infertility who are over the age of 40 years. It may also be offered as a treatment choice in those of any age who have fertility issues related to fallopian tube damage or blockage, ovulation disorders, endometriosis, uterine fibroids, previous surgery to prevent pregnancy, issues with sperm, unexplained infertility or genetic disorders and in those who wish to preserve fertility in cases of cancer or other medical conditions.

VIDEO INSIGHTS

Examining Infertility

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ICSI is often used for couples with male factor infertility and alongside IVF.⁴ In ICSI, each mature egg is injected with one healthy sperm using a needle; the resulting embryo is then transferred into the uterus.^{12,13} ICSI is most often used in cases of poor semen quality, low sperm count or if previous IVF attempts were unsuccessful.¹²

Medications Used in ART Protocols

There are a variety of medications and protocols used as a component of ART in the management of infertility. Controlled ovarian stimulation (COS) and ovulation induction therapy are essential steps in IVF and ICSI.¹⁴ Gonadotropin injections, including products containing FSH and LH, are often included in these infertility management protocols.¹⁴ Current gonadotropin injectable preparations available contain LH, FSH or a combination of both. Products may be either recombinant or purified from the urine of postmenopausal women as FSH or highly purified human menopausal gonadotropin (HP-hMG).¹⁴

Menotropin (HP-hMG)—a product with an FSH:LH ratio of 1:1—may be used to stimulate the ovaries to produce eggs; most of the LH activity in HP-hMG originates from the human chorionic gonadotropin (hCG) content.¹⁴ Like LH, hCG activity in HP-hMG binds to the LH receptor and stimulates follicle growth and maturation in the ovaries, triggering ovulation.¹⁴ Highly purified hMG is indicated for the development of multiple follicles and pregnancy in ovulatory women as part of an ART cycle.¹⁵ Injections with HP-hMG have shown favorable pregnancy outcomes in a randomized, open-label, assessor-blind, parallel group, multicenter, noninferiority trial comparing HP-hMG to recombinant human FSH (rFSH, also known as *folitropin*).¹⁶ The ongoing pregnancy rate was 30% and 27% in the HP-hMG and rFSH groups, respectively, in the per protocol (PP) group and 29% and 27%

in the intention-to-treat (ITT) population (treatment difference: PP group, 3% [95% CI, -3.8% to 9.8%]; ITT group, 2.2% [95% CI, 4.2%-8.6%]).¹⁶ In another open-label, randomized, multicenter study comparing the effectiveness of HP-hMG to rFSH in patients, the ongoing pregnancy rate was 26.3% in the HP-hMG group compared with 25.2% in the rFSH group in the ITT (p-value not significant) population and 24.8% in the HP-hMG group and 32.1% in the rFSH group in the PP population (p-value = 0.05994).¹⁷ Treatment with HP-hMG was also well tolerated by most patients; the most common side effects in patients treated with HP-hMG included ovarian hyperresponsiveness and/or ovarian hyperstimulation syndrome (OHSS) (6.1%), missed abortion (1.7%) and headache (1%).¹⁷

Gonadotropin stimulation with rFSH injection stimulates the ovaries to produce follicles.¹⁸ rFSH is indicated for induction of ovulation and pregnancy in women with anovulatory infertility in whom the cause of infertility is functional and not due to primary ovarian failure and also for pregnancy in normally ovulatory women who are undergoing controlled ovarian stimulation as part of an IVF or ICSI cycle.¹⁸ Ongoing pregnancy rates in patients receiving rFSH are listed in the paragraph above and are comparable to those with HP-hMG. The most common side effects in patients using rFSH include ovarian hyperresponsiveness and/or OHSS (13.2%), headache (1.7%) and missed abortion (1%).¹⁷ Of note, the incidence of ovarian hyperresponsiveness and/or OHSS was significantly more frequent in patients receiving rFSH compared with those given HP-hMG (6.1% vs 3.2%, respectively; p-value = 0.036).¹⁷

After maturation of follicles or in the case of IUI, an exogenous trigger injection with hCG is often administered.¹⁹ The hCG trigger shot stimulates the release of the egg and is timed to when the egg is retrieved.¹¹ The

action of an hCG trigger shot injection is similar to that of LH and has a low degree of FSH activity.²⁰ Injection induces maturation of a normal ovarian follicle and triggers ovulation.²⁰ The odds of ongoing pregnancy and live birth was significantly improved with trigger injection of hCG (194 [range, 128-281] live or ongoing pregnancies/1,000 patients) compared with placebo or no treatment (120 live or ongoing pregnancies/1,000 patients) (OR, 1.76; 94% CI, 1.08-2.86). It is notable, however, that across the three trials that included 527 patients, the quality of evidence is considered low utilizing the GRADE working group grades of evidence levels.²¹ Side effects occurring with hCG injection included headache, irritability, restlessness, depression, fatigue, edema, precocious puberty, gynecomastia and pain at injection site.²⁰

Progesterone supplementation may also be administered during ART protocols. Progesterone typically prepares the uterus for implantation by stimulating endometrial proliferation.²¹ During an ART protocol, the ovaries are stimulated in a controlled manner such that the resulting corpus luteum may not produce sufficient levels of progesterone to maintain pregnancy.²¹ Progesterone supplementation may be achieved as oral, vaginal or intramuscular supplementation during the luteal phase of the menstrual cycle.²¹ Vaginal progesterone supplementation is indicated to support embryo implantation and early pregnancy by supplementing corpus luteal function during ART for infertility in women.²² Clinical pregnancy rates exceeding 40% have been seen in a clinical trial of progesterone vaginal inserts and progesterone vaginal gel.²³ No clinically meaningful differences were seen in a study comparing progesterone vaginal inserts with progesterone vaginal gel.²³ The most common side effects with progesterone vaginal supplementation (insert or gel) included pain after oocyte retrieval, abdominal pain,

nausea and OHSS.²³ Intramuscular progesterone supplementation beginning four days prior to ET is also associated with high clinical pregnancy rates.²⁴ Higher progesterone levels achieved also result in significantly higher rates of clinical pregnancy and live births. The clinical pregnancy rate was 73.4% in the group having progesterone levels of at least 20 ng/mL compared with 56% in the group having a progesterone level less than 20 ng/mL (p-value = 0.01). Further, the rate of live births was 64.9% in the higher progesterone level group vs 50.7% in the lower progesterone level group (p-value = 0.04).²⁴

Comparison of Outcomes

With a variety of products to include in protocols, it is important to consider clinical pregnancy rates and live birth rates associated with different regimens. In a randomized, open-label, assessor-blinded, parallel-group, noninferiority trial of 620 women receiving either HP-hMG or rFSH (as follitropin alfa) undergoing ICSI, ongoing pregnancy rates were 35.5% in the HP-hMG group and 30.7% in the rFSH group (95% CI, -2.7% to 12.1%), establishing noninferiority.²⁵ Cumulative live birth rates were similar between groups (51.5% in the rFSH group and 50.6% in the HP-hMG group; 95% CI, -8.7% to 7.1%).²⁵ Pregnancy loss rates were lower in the HP-hMG group than in the rFSH group (14.5% vs 25.5%, respectively; 95% CI, -18.8% to -3.14%).²⁶ HP-hMG was associated with lower OHSS rates (21.4% in the rFSH group vs 9.7% in the HP-hMG group; 95% CI, -17.3% to -6.1%).²⁵

In additional studies comparing regimens of HP-hMG and rFSH, similar ongoing pregnancy and live birth rates were seen.^{14,25} Oocyte retrieval rates appeared to favor rFSH compared with HP-hMG in women undergoing IVF/ICSI.¹⁴ The number of oocytes retrieved were significantly higher in rFSH groups compared with HP-hMG groups in randomized open label trials (p-value < 0.001).¹⁴ The risk

of OHSS observed with HP-hMG and rFSH was similar (7% vs 5%, respectively).¹⁴ However, in one study, serious treatment-related OHSS occurred only in the rFSH group.¹⁴

A multicenter, open-label, single cohort study assessing the efficacy and safety of rFSH (in the form of follitropin delta) combined with HP-hMG compared with rFSH alone demonstrated that combination HP-hMG and rFSH protocols led to significantly better-quality oocytes and embryos, as well as good-quality usable blastocysts, compared with use of rFSH alone.²⁶ The mean (SD) number of good-quality blastocysts in the combination group was 4.9 (3.9) compared with 2.0 (2.2) in the rFSH alone group (p-value < 0.001); the mean (SD) number of oocytes retrieved in the combination group was 14.55 (7.58) compared with 7.4 (4.3) in the rFSH alone group (p-value < 0.001); and the mean (SD) number of embryos on day 3 was 8.30 (5.05) in the combination group compared with 5.4 (3.7) in the rFSH alone group (p-value < 0.001).²⁶

One study compared combined use of HP-hMG plus rFSH (as follitropin delta) with follitropin alone in patients receiving IVF who were at risk for poor ovarian response (defined as an anti-Müllerian hormone level < 2.1 ng/mL); no significant differences in rates of ongoing pregnancy (27.3% vs 28.3%; p-value = 0.739) or live births (27.3% vs 27.6%; p-value > 0.999) were noted.²⁷ Twin pregnancy rate was significantly higher in the combination group compared with the follitropin delta monotherapy group.²⁸ There was no significant difference in the incidence of OHSS between treatment groups.²⁸ In other studies comparing the efficacy and safety of follitropin delta to those of follitropin alpha/beta, the use of follitropin delta led to no differences in pregnancy rates and live birth rates compared with follitropin alpha/beta.²⁸ There was also no difference in the incidence of moderate to severe OHSS.²⁸ Follitropin delta was slightly

favorable in reducing incidence of moderate to severe early OHSS.²⁸

ART is associated with a risk of multiple births and preterm delivery, which can be mitigated by performing a single ET, and this may also decrease future risk of neurodevelopmental disorders including cerebral palsy.²⁹ ART conveys an increased risk of maternal complications such as hypertensive disorders of pregnancy, placental complications, preterm delivery and cesarean section.³⁰ ART has also been associated with various perinatal outcomes including cerebral palsy, autism, neurodevelopmental imprinting disorders and cancer, although conclusive evidence has not been established; it remains unclear whether these factors are related to ART or to other factors such as medical and environmental factors.²⁹

Economic Considerations

As with most specialty medications, there are economic considerations that must be made with infertility treatment. In a retrospective analysis of Workpartners' Research and Reference Database using data from self-insured US employees from January 2010 to December 2022 including 10,820 women (7,589 in the high-coverage cohort and 3,231 in the low-coverage cohort), high coverage levels for infertility treatment were associated with higher usage rates of ART medication and procedures (55.8% in the high-coverage cohort compared with 36.7% in the low-coverage cohort; p-value < 0.001).³⁰ In addition, there were significantly increased odds of becoming pregnant (59.9% in the high-coverage cohort vs 56.5% in the low-coverage cohort; p-value = 0.0014) and of becoming pregnant with use of any ART (69.6% vs 65.3%, respectively; p-value = 0.0089).³⁰ Improved maternal outcomes (rate of cardiomyopathy: 0.03% vs 0.27%; p-value = 0.0260) and perinatal outcomes (pediatric ICU admissions: 0.32% vs 1.06%; p-value = 0.0074) were also seen in the

high-coverage cohort compared with the low-coverage cohort.³⁰

Restricted coverage, cost-sharing in the form of deductibles, copayments, coinsurance and formulary or preauthorization requirements limit access to infertility treatment.³¹ While 19 states in the United States have legislation defining infertility as a disease and, thus, in some form codify an infertile state as an eligible condition for state-provided health insurance plan coverage, this may not be enough to guarantee coverage.³²⁻³⁴ In some states, self-funded health insurance coverage is exempt from state mandates.^{32,35,36} This accounts for 61% of workers with employer-sponsored health insurance.³⁷ State Medicaid coverage of fertility services is low, with some states covering diagnostic services but very few providing any treatment coverage.³⁸ Because of the large variations in treatment methods and medication costs, estimating the economic impact of infertility care remains challenging.³⁹ Although treatments can be a few hundred dollars, costs could reach into the tens of thousands of dollars.³⁹ These costs are out of pocket for most patients, limiting access to treatment.

A survey of patients who underwent one unsuccessful cycle of IVF found that 65.2% discontinued treatment, describing the treatment as too stressful and stating that they could not afford out-of-pocket costs.⁴⁰ This suggests that higher fertility cost coverage may lead to better outcomes. States with complete insurance coverage for IVF have much higher usage rates than do states without complete coverage.⁴¹ Live birth rates are higher in states with comprehensive or mandated coverage than in those without this coverage (35.4% vs 33.4%, respectively), with opposite trends in multiple birth rates (10.2% vs 13.8%, respectively).⁴¹ Improved access to infertility care and increased fertility benefits could decrease disparities in access to care among underserved populations such as racial and ethnic

minorities and those with lower socioeconomic resources.⁴¹

Conclusion

Infertility is a prevalent condition with causes ranging from hormonal imbalances and anatomical issues to lifestyle factors like stress and medication. Infertility often leads to emotional and psychological distress including depression and anxiety, further complicating efforts to achieve pregnancy. Several medications are used to stimulate ovulation and improve fertility outcomes, each with distinct efficacy and side effects. Treatment choice depends on individual patient needs and response. Mixed protocols combining different hormones may improve ART outcomes, especially for patients with specific fertility challenges; individualized treatment plans enhance effectiveness and reduce risks. The high costs of ART treatments, often not fully covered by insurance, limit access for many patients; coverage disparities affect treatment usage and outcomes, with better coverage leading to improved success rates and reductions in disparate access to care for underserved populations. ■

References

1. How common is male infertility, and what are its causes? National Institutes of Health. November 18, 2021. Accessed September 16, 2024. <https://www.nichd.nih.gov/health/topics/menshealth/conditioninfo/infertility>
2. Infertility: frequently asked questions. Centers for Disease Control and Prevention. May 25, 2024. Accessed August 9, 2024. <https://www.cdc.gov/reproductive-health/infertility-faq/index.html>
3. Nugent CN, Chandra A. Infertility and impaired fecundity in women and men in the United States, 2015-2019. *Natl Health Stat Report*. 2024;(202):1-19.
4. What lifestyle and environmental factors may be involved with infertility in females and males? National Institutes of Health. May 4, 2022. Accessed August 9, 2024. [tioninfo/causes/lifestyle](https://www.nichd.nih.gov/health/topics/infertility/condi-

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5. Nik Hazlina NH, Norhayati MN, Shaiful Bahari I, Nik Muhammad Arif NA. Worldwide prevalence, risk factors and psychological impact of infertility among women: a systematic review and meta-analysis. *BMJ Open*. 2022;12(3):e057132. doi:10.1136/bmjopen-2021-057132
6. Rooney KL, Domar AD. The relationship between stress and infertility. *Dialogues Clin Neurosci*. 2018;20(1):41-47. doi:10.31887/DCNS.2018.20.1/krooney
7. Massey AJ, Campbell BK, Raine-Fenning N, Pincott-Allen C, Perry J, Vedhara K. Relationship between hair and salivary cortisol and pregnancy in women undergoing IVF. *Psychoneuroendocrinology*. 2016;74:397-405. doi:10.1016/j.psyneuen.2016.08.027
8. Lynch CD, Sundaram R, Maisog JM, Sweeney AM, Buck Louis GM. Preconception stress increases the risk of infertility: results from a couple-based prospective cohort study—the LIFE study. *Hum Reprod*. 2014;29(5):1067-1075. doi:10.1093/humrep/deu032
9. Infertility. May 22, 2024. World Health Organization. Accessed August 9, 2024. <https://www.who.int/news-room/fact-sheets/detail/infertility>
10. Xie Y, Ren Y, Niu C, Zheng Y, Yu P, Li L. The impact of stigma on mental health and quality of life of infertile women: a systematic review. *Front Psychol*. 2023;13:1093459. doi:10.3389/fpsyg.2022.1093459
11. Female infertility. Mayo Clinic. August 27, 2021. Accessed August 9, 2024. <https://www.mayoclinic.org/diseases-conditions/female-infertility/diagnosis-treatment/drc-20354313>
12. In vitro fertilization (IVF). Mayo Clinic. September 1, 2023. Accessed August 9, 2024. <https://www.mayoclinic.org/tests-procedures/in-vitro-fertilization/about/pac-20384716>
13. Intracytoplasmic sperm injection: ICSI. American Pregnancy Association. 2024. Accessed August 9, 2024. <https://americanpregnancy.org/getting-pregnant/infertility/intracytoplasmic-sperm-injection/>
14. Deeks ED. Highly purified human menopausal gonadotropin (Menopur): a profile of its use in infertility. *Clin Drug Investig*. 2018;38(11):1077-1084. doi:10.1007/s40261-018-0703-8
15. Menopur. Prescribing information. Ferring

- Pharmaceuticals, Inc. May 2018. Accessed August 9, 2024. <https://d2hu1op93dom-jx.cloudfront.net/wp-content/uploads/sites/12/2021/06/24085313/Menopur-PI-Rev.-05.2018-20Mar2019.pdf>
- 16.** Devroey P, Pellicer A, Nyboe Andersen A, Arce JC; Menopur in GnRH Antagonist Cycles With Single Embryo Transfer Trial Group. A randomized assessor-blind trial comparing highly purified hMG and recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer. *Fertil Steril.* 2012;97(3):561-571. doi:10.1016/j.fertnstert.2011.12.016
- 17.** Hompes PG, Broekmans FJ, Hoozemans DA, Schats R; FIRM group. Effectiveness of highly purified human menopausal gonadotropin vs. recombinant follicle-stimulating hormone in first-cycle in vitro fertilization-intracytoplasmic sperm injection patients. *Fertil Steril.* 2008;89(6):1685-1693. doi:10.1016/j.fertnstert.2007.05.039
- 18.** Follistim. Prescribing information. Organon; 2018. Accessed August 28, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021211s027s036s042lbl.pdf
- 19.** Carson SA, Kallen AN. Diagnosis and management of infertility: a review. *JAMA.* 2021;326(1):65-76. doi:10.1001/jama.2021.4788
- 20.** Novarel. Prescribing information. Ferring Pharmaceuticals; 2023. Accessed August 9, 2024. <https://ferringusa.com/wp-content/uploads/sites/12/2023/06/NOVAREL-US-PI-REV.-05.2023-CLEAN.pdf>
- 21.** van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. *Cochrane Database Syst Rev.* 2015;2015(7):CD009154. doi:10.1002/14651858.CD009154.pub3
- 22.** Endometrin. Prescribing information. Ferring Pharmaceuticals; 2018. Accessed August 9, 2024. <https://d2hu1op93dom-jx.cloudfront.net/wp-content/uploads/sites/12/2021/06/24085312/Endometrin-PI-01-2018.pdf>
- 23.** Doody KJ, Schnell VL, Foulk RA, et al. Endometrin for luteal phase support in a randomized, controlled, open-label, prospective in-vitro fertilization trial using a combination of Menopur and Bravelle for controlled ovarian hyperstimulation. *Fertil Steril.* 2009;91(4):1012-1017. doi:10.1016/j.fertnstert.2008.01.069
- 24.** Brady PC, Kaser DJ, Ginsburg ES, et al. Serum progesterone concentration on day of embryo transfer in donor oocyte cycles. *J Assist Reprod Genet.* 2014;31(5):569-575. doi:10.1007/s10815-014-0199-y
- 25.** Witz CA, Daftary GS, Doody KJ, et al. Randomized, assessor-blinded trial comparing highly purified human menotropin and recombinant follicle-stimulating hormone in high responders undergoing intracytoplasmic sperm injection. *Fertil Steril.* 2020;114(2):321-330. doi:10.1016/j.fertnstert.2020.03.029
- 26.** Bissonnette F, Minano Masip J, Kadoch IJ, Librach C, Sampalis J, Yuzpe A. Individualized ovarian stimulation for in vitro fertilization: a multicenter, open label, exploratory study with a mixed protocol of follitropin delta and highly purified human menopausal gonadotropin. *Fertil Steril.* 2021;115(4):991-1000. doi:10.1016/j.fertnstert.2020.09.158
- 27.** Duarte-Filho OB, Miyadahira EH, Matsmoto L, Yamakami LYS, Tomioka RB, Podgaec S. Follitropin delta combined with menotropin in patients at risk for poor ovarian response during in vitro fertilization cycles: a prospective controlled clinical study. *Reprod Biol Endocrinol.* 2024;22(1):7. doi:10.1186/s12958-023-01172-9
- 28.** Komiya S, Watanabe J, Terayama T, Kamijo K, Okada H. Efficacy and safety of follitropin delta versus follitropin alpha/beta in infertility treatment: a systematic review and meta-analysis. *Reprod Med Biol.* 2024;23(1):e12573. doi:10.1002/rmb2.12573
- 29.** Graham ME, Jelin A, Hoon AH Jr, Wilms Floet AM, Levey E, Graham EM. Assisted reproductive technology: short- and long-term outcomes. *Dev Med Child Neurol.* 2023;65(1):38-49. doi:10.1111/dmcn.15332
- 30.** Guo A, Guo K, Brook R, et al. The impact of health benefit design on assisted reproductive technology utilization and pregnancy outcomes. *JMCP.* 2023;29(10-a;suppl):S113. Abstract N8.
- 31.** Health insurance coverage for infertility services, fertility preservation services, and health care services related to surrogacy. New York State Department of Financial Services. 2023. Accessed August 28, 2024. https://www.dfs.ny.gov/consumers/health_insurance/infertility_consumer_faq_052621
- 32.** Koniars KG, Penzias AS, Roosevelt J Jr, Adashi EY. The Massachusetts Infertility Insurance Mandate: not nearly enough. *FS Rep.* 2022;3(4):305-310. doi:10.1016/j.xfre.2022.08.004
- 33.** 211 CMR 37: infertility benefits. Mass.gov. 2010. Accessed September 18, 2024. <https://www.mass.gov/doc/211-cmr-37-infertility-benefits/download>
- 34.** Infertility coverage by state. RESOLVE. June 17, 2024. Accessed September 18, 2024. <https://resolve.org/learn/financial-resources-for-family-building/insurance-coverage/insurance-coverage-by-state/>
- 35.** Chirba-Martin MA, Brennan TA. The critical role of ERISA in state health reform. *Health Aff (Millwood).* 1994;13(2):142-156. doi:10.1377/hlthaff.13.2.142
- 36.** Commercial health insurance mandates: state and federal roles. National Conference of State Legislatures. Updated January 25, 2024. Accessed September 18, 2024. <https://www.ncsl.org/health/commercial-health-insurance-mandates-state-and-federal-roles>
- 37.** Weigel G, Ranhi U, Long M, Salganicoff. Coverage and use of fertility services in the US. KFF. September 15, 2020. Accessed August 28, 2024. <https://www.kff.org/womens-health-policy/issue-brief/coverage-and-use-of-fertility-services-in-the-u-s/>
- 38.** Mandated coverage of infertility treatment. KFF. 2024. Accessed August 28, 2024. <https://www.kff.org/womens-health-policy/state-indicator/infertility-coverage/?currentTimeframe=0&sort=Model=%7B%22colld%22:%22Location%22,%22sort%22:%22asc%22%7D>
- 39.** Peipert BJ, Mebane S, Edmonds M, Watch L, Jain T. Economics of fertility care. *Obstet Gynecol Clin North Am.* 2023;50(4):721-734. doi:10.1016/j.ogc.2023.08.002
- 40.** Domar AD, Rooney K, Hacker MR, Sakkas D, Dodge LE. Burden of care is the primary reason why insured women terminate in vitro fertilization treatment. *Fertil Steril.* 2018;109(6):1121-1126. doi:10.1016/j.fertnstert.2018.02.130
- 41.** Peipert BJ, Montoya MN, Bedrick BS, Seifer DB, Jain T. Impact of in vitro fertilization state mandates for third party insurance coverage in the United States: a review and critical assessment. *Reprod Biol Endocrinol.* 2022;20(1):111. doi:10.1186/s12958-022-00984-5