

## Ovarian Stimulation in Assisted Reproduction *An Educational Guide*

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### Overview

Ovarian stimulation—also known as *controlled ovarian hyperstimulation*—is a key step in assisted reproductive technologies (ART), including in vitro fertilization (IVF), surrogacy, egg freezing, and egg “donation” cycles.

In a natural menstrual cycle, one egg typically matures and is released. In contrast, ovarian stimulation uses medications to encourage the development of multiple follicles (each potentially containing an egg), increasing the number of eggs available for retrieval, fertilization, or preservation.

### How Ovarian Stimulation Works

Medications are typically administered as subcutaneous injections (shots under the skin, commonly in the abdomen or thigh) for about 7–14 days.

During this time, patients are closely monitored using:

- Ultrasound imaging (to measure follicular growth)
- Bloodwork (to track hormone levels)

Protocols vary based on:

- Age
- Ovarian reserve
- Response history or prior response to stimulation
- Clinic practices
- Protocol type (e.g., antagonist vs. agonist)

## Commonly Used Medications in Ovarian Stimulation

### 1. Gonadotropins (Primary Stimulation Medications)

These drugs directly stimulate follicle development and are typically taken as daily injections.

#### Recombinant FSH (rFSH):

- Examples:
  - Gonal-F (follitropin alfa)

- Follistim AQ/Pen (follitropin beta)
- Other brands: Bemfola, Puregon (in some regions)
- Purpose: Stimulate multiple follicle growth
- Common Side Effects:
  - Mood swings, anxiety, irritability, emotional fluctuations
  - Headache, nausea, bloating
  - Abdominal discomfort or pain
  - Injection site reactions (redness, swelling, bruising)
  - Fatigue, breast tenderness
  - Acne, rash
- Rare or Serious Side Effects:
  - Ovarian cysts or enlargement
  - Ovarian Hyperstimulation Syndrome (OHSS): severe bloating, rapid weight gain, severe nausea/vomiting, shortness of breath, decreased urine
  - Allergic reactions (rash, itching, swelling, trouble breathing)
  - Blood clots, ovarian torsion
  - Future infertility
  - Death

### **Human menopausal gonadotropins (hMG)**

- Example: Menopur (menotropins)
- Purpose: FSH + LH stimulation
- Side Effects: Similar to rFSH; may include back pain or muscle aches, menstrual changes, drowsiness

Older/less common gonadotropins: Repronex, Bravelle, low-dose hCG (sometimes used as an LH substitute in certain protocols)

## **2. GnRH Modulators (Prevent Premature Ovulation)**

These drugs, added mid-stimulation (often starting around day 5-6), prevent early LH surge and suppress natural ovulation until retrieval. That is, they prevent early ovulation during stimulation.

### **GnRH Antagonists (short-acting, common in modern protocols):**

- Examples: Ganirelix, Cetrotide
- Common Side Effects:
  - Mood swings or emotional fluctuations
  - Headache
  - Nausea
  - Injection site reactions
- Rare or Serious Side Effects:
  - Bloating or diarrhea
  - OHSS in high responders
  - Severe allergic reactions
  - Heavy vaginal bleeding

### **GnRH Agonists (used in longer "down-regulation" protocols, sometimes microdosed):**

- Examples: Lupron (leuprolide acetate), Synarel (nasal), Decapeptyl, Zoladex (less common for stim phase)
- Common Side Effects: emotional changes, hot flashes, headache, nausea or upset stomach, fatigue, injection site irritation
- Rare Side Effects: mood swings, breast tenderness, severe nausea

### **3. Trigger Shot (Final Egg Maturation)**

Administered about 36 hours prior to egg retrieval to mimic the natural LH surge.

#### **hCG Trigger(human chorionic gonadotropin):**

- Examples: Ovidrel, Pregnyl, Novarel, Profasi
- Side Effects:
  - Abdominal pain or discomfort
  - Nausea and vomiting
  - Headache
  - Injection site reactions
  - OHSS risk (higher in some patients)
- Serious Risks:
  - Blood clots
  - Pulmonary issues
  - Allergic reactions
  - Severe pelvic pain
  - Ovarian issues (infertility)
  - Severe OHSS
  - Death

#### **GnRH Agonist Trigger (for high responders):**

- Examples: Lupron (higher dose) or dual trigger (Lupron + low-dose hCG)
- Purpose: Reduces OHSS risk
- Common Side Effects:
  - Hot flashes
  - Headache
  - Nausea or upset stomach
  - Fatigue
  - Injection site irritation
- Less Common Side Effects:
  - Mood swings
  - Breast tenderness
  - Severe nausea/vomiting
  - Discomfort with intense hot flashes

## Monitoring & Safety Notes

Modern IVF protocols in the U.S. commonly use:

- FSH-based stimulation
- GnRH antagonist (e.g., Ganirelix or Cetrotide)
- hCG or GnRH agonist trigger

Some protocols may include adjuncts (e.g., growth hormone), though these are not standard.

Oral medications or drugs (e.g., Clomid/clomiphene or letrozole) are sometimes used for milder stimulation or in mini-IVF, but injections dominate true ovarian stimulation for IVF.

Protocols can be highly individualized. If preparing for or in a cycle, the clinic will provide detailed instructions, mixing guides, and injection education.

## IVF Drug Research & Long-Term Effects

There are numerous published studies and systematic reviews examining the potential toxicity (e.g., side effects, hormonal disruptions) and long-term effects of IVF drugs, such as gonadotropins (e.g., FSH like Gonal-F or Follistim, hMG like Menopur), GnRH modulators (e.g., antagonists like Ganirelix or agonists like Lupron), and triggers (e.g., hCG like Ovidrel). These investigations primarily focus on maternal health (e.g., cancer risk, cardiovascular issues, metabolic disorders) and offspring outcomes (e.g., birth defects, long-term health).

However, it is crucial to note that most available research on the safety and long-term effects of IVF drugs has focused on women undergoing treatment for infertility or older populations of women. Consequently, the findings may not fully apply to egg “donors” or individuals pursuing elective egg freezing, who are typically younger, may have different baseline health profiles, and have different ovarian response rates (e.g. older or infertile ovaries typically don’t respond as robustly as healthy, young ovaries would). Additionally, it can be difficult to distinguish the effects of fertility medications from those of underlying infertility or related conditions. Long-term, population-specific data for donors and elective fertility preservation remain extremely limited.

Because of the aforementioned, it can be difficult to distinguish the effects of fertility medications from factors related to infertility itself (such as endometriosis, nulliparity, or hormonal conditions), age, or other health variables. Additionally, long-term, population-specific data on individuals undergoing ovarian stimulation for donation or elective fertility preservation remain limited. While there is no clear evidence suggesting increased long-term risk in these groups, the relative lack of targeted research means some uncertainties remain.

*“One of the challenges in interpreting various studies is that women who receive treatment for infertility are a diverse group and their medical history and health status vary. Also, many studies group together women undergoing IVF, freezing their eggs or donating their eggs.”<sup>1</sup>*

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<sup>1</sup> <https://www.arcfertility.com/are-fertility-drugs-safe-yes-according-to-evidence-to-date/>

Below is a brief summary of key findings from major studies and reviews.

### **Maternal Health**

Studies often assess risks like cancer (hormone-sensitive types such as ovarian, breast, or endometrial), cardiovascular disease, metabolic issues, and bone health, given the drugs' temporary elevation of hormones like estrogen.

### **Cancer Risk**

Guidelines from the American Society for Reproductive Medicine (ASRM, 2024) reviewed multiple studies and concluded that “there does not appear to be a” link between IVF drugs and breast, colon, cervical, or uterine cancer.

There is ongoing investigation into possible associations with ovarian and thyroid cancers. Interpretation of these findings is complicated by confounding factors such as underlying infertility, delayed childbearing, and related conditions.

*“Methodological limitations in studying the association between the use of fertility drugs and cancer include the inherent increased risk of cancer in women who never conceive, the increased risk of cancer because of factors (endometriosis and unopposed estrogen) associated with infertility, the low incidence of most of these cancers, and that the diagnosis of cancer is typically several years after fertility drug use. On the basis of available data, there does not appear to be an association between fertility drugs and breast, colon, or cervical cancer. There is no conclusive evidence that fertility drugs increase the risk of uterine cancer, although women with infertility are at higher risk of uterine cancer. There are insufficient data to comment on the risk of melanoma and non-Hodgkin lymphoma associated with fertility drug use. Women should be informed that there may be an increased risk of invasive and borderline ovarian cancers and thyroid cancer associated with fertility treatment. It is difficult to determine whether this risk is related to underlying endometriosis, female infertility, or nulliparity. (Fertil Steril® 2024;122:406–20. ©2024 by American Society for Reproductive Medicine.)”<sup>2</sup>*

Large cohort studies generally align with these conclusions, though continued long-term follow-up is needed as methodological limitations are noted.

### **Cardiovascular and Metabolic Risks**

Some studies suggest possible associations between fertility treatment and cardiovascular or metabolic conditions, but findings are inconsistent and limited. No definitive causal relationship has been established.

### **Other Long-Term Effects**

Some current evidence does not demonstrate significant long-term effects on bone density or endocrine health. However, research remains ongoing, particularly in populations outside of infertility treatment. Hormonal stimulation cycles can cause short-term elevations in estrogen

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<sup>2</sup> <https://www.asrm.org/practice-guidance/practice-committee-documents/fertility-drugs-and-cancer-a-guideline-2024>

levels, and while these changes are generally considered temporary, the long-term implications of repeated exposure are not yet fully understood. Individuals with hormone-sensitive conditions, such as PCOS<sup>3</sup> or endometriosis<sup>4</sup>, may require additional consideration, although evidence regarding long-term effects in these groups remains limited.

Further long-term, population-specific research is needed to better understand potential risks and outcomes.

## Offspring Health

Research on children conceived through assisted reproductive technologies (ART) is often included in discussions of IVF. However, it is important to note that most of these studies evaluate outcomes associated with the entire IVF process—not the isolated effects of ovarian stimulation medications, which is the focus of this document.

Factors such as, but not limited to:

- Underlying infertility
- Parental age and health
- Laboratory conditions and embryo culture
- Use of intracytoplasmic sperm injection (ICSI)
- Higher rates of multiple pregnancies

can all influence outcomes, making it difficult to determine whether any observed differences are related specifically to fertility medications.

At present, there is **no conclusive evidence that ovarian stimulation drugs independently cause adverse long-term health outcomes in offspring**, and isolating their specific effects remains an area of ongoing research.

## Limitations of Current Research

- Many studies focus primarily on individuals with infertility
- Underlying infertility and associated conditions may independently affect health outcomes
- Data on surrogate mothers, egg “donors”, and individuals undergoing elective egg freezing remain limited, particularly regarding long-term outcomes. Egg donors and women who choose to freeze their eggs are typically healthy and highly responsive to fertility medications, which distinguishes them from populations undergoing treatment for infertility. Because of these differences, findings from infertility research may not fully apply to these groups, and additional population-specific studies are needed. Egg “donors”, in particular, are undergoing procedures with unknown risks and reproductive outcomes with no benefit to their own health.

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<sup>3</sup> <https://pmc.ncbi.nlm.nih.gov/articles/PMC9985778/>

<sup>4</sup> <https://academic.oup.com/humrep/article/40/7/1249/8128086?login=false>

- Egg freezing has become increasingly common in recent years; however, it was only relatively recently reclassified from an experimental procedure, and despite growing use, evidence on long-term safety, effectiveness, and outcomes remains limited, with ongoing uncertainty about potential risks and benefits.<sup>5</sup>
- Large-scale, long-term studies will be important to provide more comprehensive information for patients and healthcare providers.

## Other References and Further Reading

- <https://cbc-network.org/issues/making-life/making-life-2/>
- <https://cbc-network.org/wp-content/uploads/2023/05/Comprehensive-Paper-on-ART-Final.pdf>
- <https://pmc.ncbi.nlm.nih.gov/articles/PMC11594443/>
- <https://www.cmaj.ca/content/189/10/E391>
- <https://chatelaine.com/health/long-term-impact-ivf/>

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<sup>5</sup> <https://www.perplexity.ai/search/was-egg-freezing-ever-studied-m8BsCv1CQGKyI9dTI6sRyw>