International Journal of Research in Pharmacology & Pharmacotherapeutics (IJRPP)

IJRPP |Vol.15 | Issue 1 | Jan - Mar -2026

www.ijrpp.com

ISSN: 2278-2648

DOI : https://doi.org/10.61096/ijrpp.v15.iss1.2026.407-412

Review

Evaluation of Abnormal Gestation Induced by Corticostroids in Ivf [In Vitro Fertilisation] Procedure

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Published on:
14.03.2026

Published by:
Futuristic Publications

Abstract

Corticosteroids in IVF – Benefits and Risks: Corticosteroids like prednisolone and dexamethasone are utilized in IVF to enhance implantation by suppressing maternal immune responses and reducing uterine inflammation. While effective for patients with recurrent failure or autoimmune disorders, their use remains controversial due to significant maternal and fetal complications. Fetal risks include Intrauterine Growth Restriction (IUGR), neonatal adrenal suppression, and congenital anomalies such as orofacial clefts or clubfoot. Furthermore, steroids can weaken the amniotic sac's collagen structure, increasing the risk of Premature Rupture of Membranes (PROM) and neonatal sepsis.
Maternally, prolonged use is associated with gestational diabetes, hypertension, and Cushingoid features like fluid retention and weight gain. Paradoxically, inappropriate steroid levels can disrupt the hormonal balance needed to sustain pregnancy, potentially leading to miscarriage. Due to these risks, safer immunomodulatory alternatives including IVIG, Tacrolimus, Hydroxychloroquine, and Intralipid therapy are increasingly preferred. When combined with nutritional support (Vitamin D, Omega-3s) and anti-inflammatory lifestyle adjustments, these alternatives aim to improve reproductive success while prioritizing maternal-fetal safety and reducing systemic side effects.

Keywords: IVF, Corticosteroids; Immune Modulation; Implantation Success; FGR/IUGR, PROM, Gestational Diabetes; Preeclampsia; Congenital Anomalies; Adrenal Suppression, Placental Insufficiency; Immunomodulatory Alternatives (IVIG/Tacrolimus/HCQ)

1. INTRODUCTION

Corticosteroids are sometimes used during in vitro fertilization (IVF) to suppress the immune system and reduce inflammation, which may improve embryo implantation. They help in creating a more favorable environment in the uterus by reducing natural killer (NK) cell activity and inflammation that might otherwise reject the embryo. Common corticosteroids used in IVF include prednisone, dexamethasone and betamethasone. These drugs may be prescribed before or after embryo transfer depending on the patient's immune profile or history of IVF failure (1). While corticosteroids can enhance the chances of successful implantation in some women, their use is still controversial and not universally recommended for all IVF patients. Research results are mixed, and more high-quality studies are needed to confirm consistent benefits.

However, corticosteroids also carry potential side effects. Short-term use may lead to insomnia, mood swings, and increased blood sugar levels. Prolonged or high-dose usage can suppress adrenal function, weaken the immune system, increase infection risk, and affect bone density. For women undergoing IVF, careful dosage and duration must be monitored by a fertility specialist (2, 3).

1.1. Conditions Requiring In Vitro Fertilization (Ivf)

1.1.1. Blocked or Damaged Fallopian Tubes

IVF bypasses the tubes entirely, allowing fertilization to occur in a lab when natural pathways are blocked by scarring or infection (4).

1.1.2. Male Factor Infertility

When sperm count or motility is low, IVF (often with ICSI) ensures fertilization by manually joining the sperm and egg (5).

1.1.3. Ovulation Disorders

For conditions like PCOS, IVF uses controlled medication to produce multiple mature eggs when natural ovulation is irregular or absent (6).

1.1.4. Genetic Disorders

IVF allows for Preimplantation Genetic Testing (PGT), ensuring only embryos free of known inherited diseases are transferred to the uterus (8).

1.1.5. Endometriosis

When tissue growth causes inflammation or scarring that prevents natural conception, IVF offers a direct path to pregnancy.

1.1.6. Unexplained Infertility

In cases where no clear cause is found after extensive testing, IVF provides a highly controlled environment to overcome undiagnosed barriers.

1.1.7. Advanced Maternal Age

To counter the natural decline in egg quality and quantity after age 35, IVF maximizes the chance of success through intensive egg retrieval or donor options (7).

1.1.8. Previous Failed Fertility Treatments

If simpler methods like fertility drugs or IUI have repeatedly failed, IVF is the next logical step with significantly higher success rates (9).

1.1.9. Uterine or Cervical Issues

Structural issues like fibroids or hostile cervical mucus can block sperm; IVF bypasses these by placing the embryo directly into the uterine cavity.

1.1.10. Fertility Preservation or Cancer Treatments

Patients undergoing chemotherapy or radiation can use IVF to freeze eggs or embryos, protecting their ability to have children in the future.

2. CORTICOSTEROIDS IN IVF

Corticosteroids are synthetic hormones used in IVF to improve success rates through their anti-inflammatory and immunosuppressive properties.

Immune Modulation: Suppresses the mother's immune system to prevent it from attacking the embryo.

Reduced Inflammation: Lowers uterine inflammation to create a more receptive lining for implantation.

Classification (10):

i. Glucocorticoids

These regulate metabolism and suppress the immune system. In IVF, they are used to assist embryo implantation.

- Prednisolone
- Dexamethasone
- Hydrocortisone

ii. Mineralocorticoids

These regulate salt and water balance to maintain blood pressure. They are primarily used for adrenal insufficiencies.

- Fludrocortisone,
- Deoxycorticosterone.

2.1. Fetal Risks of Continued Corticosteroid Use in IVF and Pregnancy

The use of corticosteroids like Prednisolone and Dexamethasone in IVF and pregnancy carries several risks to fetal development and neonatal health.

2.1.1. Fetal Growth Restriction (FGR)

Long-term exposure can interfere with the growth hormone axis and reduce placental nutrient transport,

often resulting in low birth weight and respiratory issues.

2.1.2. Neonatal Adrenal Suppression

Continuous use mimics natural cortisol, suppressing the fetal HPA axis. This can cause newborns to suffer from low blood sugar, low blood pressure, and poor stress responses.

2.1.3. Orofacial Cleft

Exposure during the first trimester (weeks 4–10) may disrupt facial tissue fusion, increasing the risk of congenital malformations like cleft lip or palate (11, 12).

2.1.4. Suppression of the HPA Axis

Prolonged high doses decrease the body's natural cortisol production. This can lead to adrenal insufficiency or a life-threatening adrenal crisis during the stress of delivery.

2.1.5. Reduced Fetal Movement and CNS Effects

Steroids can impact the central nervous system, leading to decreased fetal activity. This reduction may signal altered brain development and requires intensive monitoring.

2.1.6. Neurodevelopmental and Behavioral Disorders

In-utero exposure may affect brain regions responsible for attention and memory, potentially increasing the risk of ADHD and cognitive delays in childhood.

2.1.7. Neonatal Sepsis Risk

Because steroids suppress the immune system, exposed newborns are more susceptible to early-onset infections and sepsis, particularly if born prematurely.

2.1.8. Premature Birth Risks

While some steroids aid lung maturity, long-term systemic use can paradoxically increase the risk of preterm birth by disrupting hormonal and immune balances.

2.2. Maternal Risks of Continued Corticosteroid Use in IVF and Pregnancy

2.2.1. Hypertension and Preeclampsia

Steroids cause fluid retention and elevated blood pressure, increasing the risk of preeclampsia and the potential need for early delivery (1, 3).

2.2.2. Weight Gain and Obesity

Increased appetite and fluid retention lead to excessive weight gain, which can complicate labor and increase the risk of sleep apnea.

2.2.3. Increased Susceptibility to Infections

Immune suppression makes mothers more prone to UTIs, respiratory infections, and oral thrush, which may be more severe and harder to treat.

2.2.4. Osteoporosis and Bone Pain (13)

Interference with calcium absorption can cause bone demineralization and joint pain, potentially leading to early-onset osteoporosis.

2.2.5. Mood Disorders and Sleep Disturbance

Alterations in neurotransmitters can trigger anxiety, depression, and insomnia, worsening the emotional stress of the IVF process.

2.2.6. Cataracts and Vision Changes

High-dose or prolonged use increases the risk of cataracts and vision disturbances, such as blurred vision or light sensitivity (14).

2.2.7. Skin Fragility and Stretch Marks

Weakened collagen makes skin more susceptible to severe stretch marks, bruising, and tearing as the pregnancy progresses.

2.2.8. Uterine and Tissue Weakening

Impaired wound healing and weakened tissue can complicate C-section recovery and theoretically increase the risk of uterine rupture.entially leading to early-onset osteoporosis (3).

2.3. Anomalies in Mother and Fetus Due to Corticosteroid Use in IVF:

2.3.1. Gestational Diabetes (GDM)

Steroids like Prednisolone (5–20 mg) and Dexamethasone (0.5–2 mg) can cause insulin resistance and steroid-induced diabetes, even in women with no prior history of high blood sugar (14).

2.3.2. Cryptorchidism

First-trimester exposure is linked to an increased risk of undescended testicles in male infants, where the testes fail to move from the abdomen into the scrotum.

2.3.3. Talipes Equinovarus (Clubfoot)

Corticosteroid use during IVF cycles is associated with a higher incidence of clubfoot, a congenital deformity where the newborn's foot is twisted out of position.

2.3.4. Hypertension and Preeclampsia

Steroids cause fluid retention and elevated blood pressure. This increases the risk of preeclampsia, a serious condition characterized by new-onset hypertension after 20 weeks (15).

2.3.5. Adrenal Suppression

Prolonged use suppresses the HPA axis, preventing the adrenal glands from producing natural cortisol. This can lead to a dangerous inability to respond to the physical stress of labor or illness (14).

2.3.6. Neonatal Sepsis

In-utero exposure to immunosuppressive steroids increases the risk of neonatal bloodstream infections (sepsis), which is a leading cause of morbidity in premature infants.

2.4. Corticosteroids in IVF: Key Risks of Miscarriage:

Corticosteroids, (e.g., prednisolone and dexamethasone) are used to prevent embryo rejection, inappropriate or prolonged use can paradoxically lead to pregnancy loss through several pathways.

2.4.1. Hormonal Disruption & Progesterone Interference

- **HPA Axis Suppression:** Steroids can disrupt the hormonal balance necessary for early pregnancy.
- **Progesterone Impact:** They may reduce natural progesterone synthesis or impair the uterine lining's responsiveness to it, destabilizing the pregnancy even if supplements are used.

2.4.2. Immunological Imbalance

- **Over-Suppression:** Pregnancy requires a "fine balance." Excessive suppression can block the essential immune signaling needed for the body to tolerate the embryo and develop the placenta.
- **Disrupted Dialogue:** In patients without immune issues, unnecessary steroid use disrupts the natural immunological processes that support implantation.

2.4.3. Placental Insufficiency

- **Vascular Impairment:** High doses can interfere with angiogenesis (the growth of new blood vessels) and trophoblast invasion.
- **Resource Deprivation:** Poor placental development leads to a lack of oxygen and nutrients, resulting in growth restriction or missed miscarriage.

2.4.4. Embryo Toxicity & Development

- **Cellular Damage:** High steroid exposure during the first trimester may trigger apoptosis (cell death) during critical organ formation.
- **Early Death:** Even if no visible birth defects occur, developmental interruptions can lead to early embryonic death and miscarriage.
- 5. Infection Susceptibility:
- **Suppressed Immunity:** Steroids make the mother more prone to infections like bacterial vaginosis or chronic endometritis.
- **Silent Risks:** These infections can go undiagnosed due to masked symptoms, eventually triggering first or second-trimester loss (16).

2.5. Corticosteroid Use in IVF and Fetal Premature Rupture of Membranes (PROM):

2.5.1. Immunomodulatory Role & Risk

While corticosteroids (e.g., prednisolone) help prevent embryo rejection by suppressing maternal immune responses (like NK cells), prolonged use can increase the risk of Premature Rupture of Membranes (PROM).

2.5.2. Structural Fragility

Excessive steroid exposure may interfere with collagen synthesis and the extracellular matrix, making the amniotic sac (amnion and chorion) brittle and more prone to tearing before labor begins.

2.5.3. Clinical Dangers

Rupture before 37 weeks (PPROM) leads to amniotic fluid loss, increasing the risk of intrauterine infection (chorioamnionitis), placental abruption, and fetal distress) (17).

2.6. Understanding Premature Rupture of Membranes (PROM)

2.6.1. Definition and Anatomy

PROM is the rupture of the amnion and chorion (the protective layers surrounding the fetus) before labor begins, compromising the amniotic fluid and structural support necessary for fetal development.

2.6.2. Risks and Steroid Impact

Rupture can lead to severe complications like intrauterine infection (chorioamnionitis), placental abruption, and fetal distress, with prolonged corticosteroid use in IVF potentially contributing to membrane fragility and structural weakness.

2.6.3. Mechanism: How Corticosteroids May Contribute to PROM

- Altered Collagen Synthesis and Membrane Weakening.
- Suppression of Immune Responses and Increased Infection Risk
- Impact on Amniotic Fluid Regulation.
- IVF as a High-Risk Baseline.

2.6.4. Timing and Duration

First-trimester use can disrupt organogenesis, while prolonged exposure beyond 12 weeks reduces growth velocity, leading to measurable reductions in birth size and weight.

2.6.5. Nutrient Transfer

Steroids can thicken the placental barrier and impair the transport of glucose and oxygen, causing asymmetric growth restriction where the body is smaller than the head.

2.6.6. Placental Surface Area

Reduced trophoblast invasion decreases the available surface area for maternal-fetal exchange, resulting in lower fetal weight gain even in full-term pregnancies.

2.7. Increased Risk of Preterm Birth and Low Birth Weight:

2.7.1. Fetal Weight Loss (Growth Restriction)

Prolonged or high-dose exposure can lead to Intrauterine Growth Restriction (IUGR) through:

- **Placental Insufficiency:** Steroids impair blood flow and nutrient transport (glucose/oxygen), starving the fetus of growth essentials.
- **Hormonal Suppression:** They cross the placenta to suppress IGF-1, a hormone critical for cell division and tissue mass.
- **Asymmetric Growth:** Chronic exposure often results in a smaller body relative to head size, increasing the risk of infants falling below the 10th percentile.

2.7.2. Preterm Birth & Low Birth Weight (LBW)

- **Shortened Gestation:** IVF pregnancies are already at risk; steroids can exacerbate this, leading to early delivery.
- **Neonatal Impact:** LBW infants have less time to accumulate fat and often require NICU care for breathing and feeding difficulties.

2.7.3. Maternal Weight Gain

Conversely, the mother often experiences weight gain due to

- **Metabolic Shifts:** Steroids increase appetite and can induce insulin resistance or gestational diabetes.
- **Physical Changes:** Common side effects include fluid retention and Cushingoid features, such as central obesity and a moon face appearance.

2.8. Alternatives to Corticosteroids in IVF

2.8.1. Intravenous Immunoglobulin (IVIG)

Concentrated antibodies that balance immune activity and reduce harmful autoantibodies; effective for recurrent miscarriage and high NK cell activity (18).

2.8.2. Tacrolimus

A potent inhibitor that blocks T-cell activation and inflammatory cytokines; specifically used for patients with elevated Th1/Th2 ratios.

2.8.3. Hydroxychloroquine (HCQ)

A safer, long-term option for women with autoimmune markers (like ANA); stabilizes lysosomes and reduces inflammation with fewer side effects than steroids.

2.8.3. Intralipid Therapy

A soybean-based emulsion that downregulates NK cell cytotoxicity; generally well-tolerated and often used to improve uterine receptivity.

2.8.4. LMWH & Low-Dose Aspirin

Standard alternatives for women with clotting disorders or poor uterine blood flow to support stable implantation.

2.8.5. Nutritional Support (Vitamin D & Omega-3s)

Essential for shifting the immune profile to a pregnancy-friendly state and providing natural anti-inflammatory effects (19).

2.8.6. Anti-Inflammatory Lifestyle

Focusing on a diet rich in healthy fats and antioxidants, stress management, and sleep hygiene to lower chronic systemic inflammation.

3. CONCLUSIONS

IVF with corticosteroids boosts implantation but risks abnormal gestation, including fetal growth restriction, anomalies, hormonal issues, and placental problems from improper dosing. IVF also raises multiple pregnancies, preterm birth, and low birth weight. Careful patient selection, dosing, and monitoring are vital to ensure maternal-fetal safety. More research is needed for safer protocols.

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