

# The Impact of Assisted Reproductive Techniques on the Risk of Multiple Pregnancies

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## ABSTRACT

**Background & Objective:** There is a well-established link between multiple pregnancies and assisted reproductive techniques (ARTs). Increased maternal and perinatal morbidity and mortality are directly related to multiple pregnancies. The purpose of the current study is to examine the effects of multiple pregnancies on women using various reproductive techniques.

**Materials & Methods:** This study used a comparative-analytical approach. We assessed a cohort of 130 pregnant women of which 120 had twins and 10 had triplets. In vitro fertilization and embryo transfer (IVF-ET) were performed on 62.0% of women, while 6.0% had ovulation induction. Using ultrasound examination, twin and triplet pregnancies were found in 92% and 8%, respectively.

**Results:** Our results show that 11% of women experience the physiological course of pregnancy with multiple pregnancies. Pregnancy concludes in the delivery of twins only in 50% of patients with multiple pregnancies diagnosed by ultrasound examination before 10 weeks. It was found that 46% of births in women carrying multiple pregnancies happened prematurely after studying more than 100 births. Of these, 6% occurred before 28 weeks, 20% between 29 and 34 weeks, and 20% between 35 and 37 weeks.

**Conclusion:** Preeclampsia and placental insufficiency are more likely to occur in multiple pregnancies than in single pregnancies. As a result, at the beginning of the second trimester, all preventative measures should be implemented. Although abdominal delivery is not the preferred option for multiple pregnancies, there is a need to increase the indications for surgical delivery for the benefit of the fetuses.

**Keywords:** Congenital Malformations, Conjoined Twins, Multiple Pregnancy, Postpartum Period



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## Introduction

Multiple pregnancies are a critical issue in obstetric and gynecological care due to an increased risk of morbidity and mortality, an increase in the number of cesarean sections and related complications in the postpartum period, and a high frequency of neurological disorders (1-3). The number of women with multiple pregnancies is steadily increasing due to the widespread use of assisted reproductive techniques (ARTs) (4, 5).

The employment of ART for fertility treatments has increased dramatically in recent years. The Centers for Disease Control and Prevention (CDC) state that 312,758 ART operations were performed in total in 2021. These surgeries produced 68,367 live-birth deliveries and 81,176 infants (2). Pregnancies after ART are linked to an increased risk of poor perinatal outcomes, according to a number of studies (6, 7). ART necessitates the treatment of sperm, eggs, or both

outside of the human body. ART includes in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), fresh or frozen/thawed embryo transfer (ET), IVF with donor oocytes, and intrauterine insemination either with ovarian stimulation using gonadotropins or oral medications such as clomiphene (OS-IUI) or in unstimulated cycles (IUI).

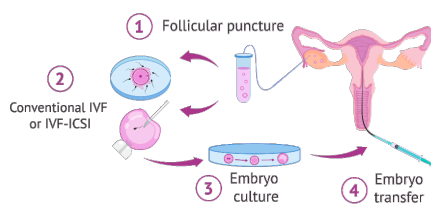
Some difficulties documented with ART are placenta previa, low birth-weight infants, cesarean delivery (CD), preterm labor, hypertensive disorders, and gestational diabetes mellitus (8). Women with multiple pregnancies are at high risk of complications during gestation and childbirth. The share of multiple pregnancies against the background of the use of ART accounts for 35.0-55.0% (9-12). Infant mortality in multiple pregnancies is 8-10 times higher than in single pregnancies, primarily due to miscarriage (13, 14). Multiple pregnancies are connected with poor

pregnancy outcomes, yet many infertile patients view it as the best possible outcome of their treatment.

The purpose of the current study is to examine the effects of multiple pregnancies on women using ARTs.

## Methods

This study used a comparative-analytical approach. We assessed a cohort of 130 pregnant women of which 120 had twins and 10 had triplets. The gestation period was 22–37 weeks. The subjects of this study were aged between 18–28 years (20.0%), 29–35 years (56.0%), 36 years and older (34.0%). In vitro fertilization and embryo transfer (IVF-ET) were performed on 62.0% of women (Figure 1), while 6.0% had ovulation induction.



**Figure 1.** The process of in vitro fertilization and embryo transfer (IVF-ET)

The evaluation of anamnesis data, as well as the findings of clinical, instrumental, and laboratory research methods, form the basis for the diagnosis of multiple pregnancies. The accuracy of the diagnosis of multiple pregnancy and the timing of its development are crucial factors in determining how it will affect the mother and fetus (15).

The most accurate way to diagnose multiple pregnancies is still ultrasound examination. Ultrasound (also called sonography or ultrasonography) can detect multiple pregnancies in the first trimester as early as 5–6 weeks. When compared to a singleton, the excretion of human chorionic gonadotropin (hCG), the level of placental lactogen, and the blood concentration of fetoprotein are all 2 times higher in the 10th week. In the second trimester, uterine growth is frequently found to be faster than what is typical for this stage of pregnancy.

In this study, twin and triplet pregnancies were found in 92% and 8%, respectively. The course of a multiple pregnancy differs from a single pregnancy in a number of negative ways because the pregnant woman's body is subjected to heavier loads with multiple pregnancies than with single pregnancies. Hemodynamics, hypovolemia, and other abnormalities appear early in the course of the pregnancy. Multiple pregnancies result in a 50–60% rise in circulating blood volume (BCC), compared to a 40–50% increase in single pregnancies (16, 17). Shortness of breath, exhaustion, and tachycardia occur because the diaphragm is forced to move in response to a greatly enlarged uterus. Varicose veins of the extremities,

and rectal veins are common as a result of inferior vena cava compression.

## Results

According to our findings, 11% of women go through the physiological stages of pregnancy while carrying multiple children. Pregnancy concludes in the delivery of twins only in 50% of patients with multiple pregnancies diagnosed by ultrasound examination before 10 weeks. This discrepancy is explained an embryo fails to develop in the early stages of pregnancy (blighted ovum). Some of the significant problems during their pregnancy are listed in Table 1:

**Table 1.** Significant problems during multiple pregnancies

| Complication                         | %  |
|--------------------------------------|----|
| Preeclampsia                         | 24 |
| Polyhydramnios                       | 16 |
| Premature Amniotic Fluid Discharge   | 26 |
| Isthmic-Cervical Insufficiency (ICN) | 34 |

Preeclampsia typically develops earlier and is more severe in pregnant women who are carrying multiple babies as opposed to just one. The prevalence of anemia in twin-pregnant women is 78%, and an increase in intravascular volume is partly linked to anemia. The function of the pelvic organs is sometimes compromised when varicose veins form in the lower extremities (18). Multiple pregnancies increase the risk of certain issues that are less common with single pregnancies, including the following: twin-to-twin transfusion syndrome (TTTS), also known as fetofetal transfusion syndrome (FFTS), twin reversed arterial perfusion (TRAP), conjoined twins, intrauterine fetal death (IUFD), and congenital anomalies (according to our data – 4%) (19, 20).

Fetal abnormalities are more common in monozygotic fetuses and are 2 times more common in women carrying multiple pregnancies than in women carrying a single pregnancy. Conjoined twins are a type of monozygotic twins. That is, they originate as a single zygote that splits into two. The most frequent varieties of conjoined twins are craniopagus (6%), parasitic twins (10%), omphalopagus (10%), thoracopagus (18.5%), and thoraco-omphalopagus (28%) (21). In this study, female fetuses make up 7.5% of conjoined twins. Although this pathology can be detected by ultrasound as early as the first trimester, the best window for its identification is between 24 and 28 weeks of gestation. Use of alternative diagnostic techniques, such as X-ray and amniography, is advised if a precise diagnosis is challenging. The condition known as FFTS frequently appears between 15 and 25 weeks after conception. Vascular anastomoses in the placenta, which promote abnormal blood flow from

one fetus to another, most frequently to the placenta of monochorionic (identical) twins, are the cause of TTTS or FETS (22). As a result, one fetus is a recipient and has dropsy due to blood volume overload, cardiomegaly, tricuspid regurgitation, ventricular hypertrophy, and obstruction of the right ventricular outlet tract, while the other becomes a donor and has a severe delay in intrauterine development.

Vascular anastomoses are nearly always present in monochorionic pregnancies (49-100% of cases). There are two types of vascular anastomoses: superficial and deep. The superficial ones are located on the chorionic plate and can be arterioarterial and venovenous. Surface anastomoses connect two systems of hemocirculation directly, they function in two directions. There are deep anastomoses when arterial blood from one fetus enters the cotyledon, and venous drainage is carried out into the circulation system of another fetus. Thus, in a monochorionic pregnancy, there is blood circulation between the fetuses, but all anastomoses function in two directions (20, 23). A single arteriovenous anastomosis with blood flowing just in one direction and a dearth of superficial anastomoses that serve as a blood bypass surgery backup are the placenta's distinguishing features in FETS. The diagnosis of FETS is usually established during ultrasound examination based on the identification of the following criteria: one placenta, a thin amniotic septum, the same sex of the fetus, a difference in the amount of amniotic fluid, detection of abnormal blood flow in the placenta using color Doppler mapping and energy Doppler. It has been suggested recently to correct FETS intrauterinally by using endoscopic access to execute vascular coagulation between the donor and recipient fetuses. Hospitalization at an obstetric facility is required if preeclampsia or other pregnancy problems start to manifest. The patient should be admitted to the maternity hospital two to three weeks before delivery in a straightforward pregnancy, and four weeks before delivery in the event of triplets.

A thorough analysis of the literature on women with a multiple pregnancy indicated that up to 68% of pregnant women worldwide suffer from iron deficiency, which is a nutritional issue (24-26). For pregnant women who have undergone IVF-ET, ovulation induction, or who have a monochorionic type of placentation, the occurrence of multiple pregnancies should be considered a high-risk factor for the development of maternal, postnatal morbidity, and mortality. As a result, every woman who has had multiple pregnancies needs a customized management strategy.

When analyzing data on patients of our center, IVF-ET was performed on 62.0% of women, while 6.0% had ovulation induction. It is important to highlight the age breakdown of the women in this study, who range in age from 18 to 28 years (20%), 29 to 35 years (56%), and 36 years and older (24%). It is recommended that

a woman be provided selective reduction if she has four or more fetuses in her uterus; the ideal time for this procedure is between eight and nine weeks of pregnancy. Recently, our clinic has not performed any transfers of more than two embryos into the uterus.

It was found that 46% of births in women carrying multiple pregnancies happened prematurely after studying more than 100 births. Of these, 6% occurred before 28 weeks, 20% between 29 and 34 weeks, and 20% between 35 and 37 weeks. In order to stop premature birth, a series of actions are taken to address growing placental insufficiency. The use of surgical delivery via caesarean section is currently becoming more common due to the significance of protecting each child's life and health. Given that the danger of prenatal fetal death from placental insufficiency grows significantly with increasing gestational age, it is prudent to broaden the reasons for surgical delivery when triplets are present at 34 weeks and when there are four or more fetuses at 32 weeks or more. It has been established that scheduled cesarean sections are linked to increased perinatal mortality when compared to vaginal births, primarily because of respiratory distress syndrome and a high incidence of neonatal problems. Following the vaginal delivery of the first fetus, it is allowed to undergo a cesarean section procedure to extract the second fetus. This is indisputable and appropriate in an emergency case since it symbolizes a delicate delivery that protects the interests of the second fetus. The method of delivery depends on the number of fetuses, their presentation, gestational age, and the presence of pregnancy complications. The course of childbirth with twins is frequently problematic from the start. For example, during the era of disclosure, the enlarged, thinner muscles of the uterus cause problems and the delivery forces become feeble, delaying the period of disclosure. The key criteria defining the aspects of the treatment of the first period of labor are the stage of pregnancy, the state of the fetus, the form of labor, and the integrity of the fetal membrane. In the event of a premature pregnancy (28-36 weeks) and the commencement of labor, childbirth should be performed in accordance with the guidelines of premature birth.

The first period strategies are the same for full-term multiple pregnancies as they are for single pregnancies. Antispasmodics, analgesics, and epidural anesthetic are frequently used during labor, and bleeding prevention is required in the immediate postoperative period. To prevent the second fetus from dying from blood loss through the first fetus's umbilical cord in the case of identical twins with a monochorionic placentation, the maternal and fetal ends of the umbilical cord are both tightly bandaged after the first fetus is born. With a two-child pregnancy, delivery at a period of less than 36 weeks has to be performed 2 times more often than with a single pregnancy.

After the 11th week of pregnancy, a fetal reduction with trans-abdominal ultrasound-assisted delivery is typically advised, while it is possible up until the 24th week. Transabdominal sonography is used to determine the position of the fetuses after prep and drape and general anesthesia. The fetus's chest is then targeted using a guide and puncture line. According to the fetus's age, 0.5 to 3 ml of 10% potassium chloride is injected into its chest cavity via a sonolucent needle, and after a few minutes, the fetal heart stops beating. The fetal heart can be assessed with the aid of echo in cases where there is uncertainty over the accuracy of the procedure. After stopping the heart of the first fetus, the same needle is used to reduce the others. The instructions before and after the reduction of the number of embryos are the same as the reduction of the embryo by transvaginal method. The instructions before to and following the decrease in the number of embryos are the same as those for the transvaginal method of embryo reduction. It should be noted that the vaginal route has a reported abortion and fetus loss rate of 2-10%, which is lower than the abdominal route. It goes without saying that the likelihood of miscarriage and premature delivery will raise as the number of decreased embryos rises.

According to reports, the risk of disseminated intravascular coagulation (DIC) rises when fetal reduction occurs at high gestational ages. Alpha-fetoprotein (AFP) levels in the mother's serum rise when the fetus is reduced. This is because the mother absorbs the contents of the fetus inside the uterus, and it should not be interpreted as a sign of neural tube abnormalities. AFP, karyotype, and cholinesterase testing should be reserved for follow-up.

Placental abruption before the birth of the second fetus leads to its intrauterine death. There may also be issues like the second fetus being in the transverse position, twins colliding, bleeding during the third stage of labor or postpartum hemorrhage (PPH), delayed uterine involution, and infectious diseases. When the cervix is opened by 4 cm and the amniotic fluid is slowly removed, it indicates the presence of polyhydramnios and the fetal membrane should be opened (within 1-2 hours).

A fetal membrane autopsy of the second fetus should be performed as soon as the first fetus is delivered in order to reduce complications in childbirth with multiple births. Experts should also start an intravenous drip of oxytocin right away in order to hasten the second stage of labor and placenta separation. The risk of bleeding increases during the third stage of labor and the first few days after delivery. Following birth, a thorough examination is performed to establish the integrity of the lobules and shells, as well as the type of twins (single or double).

The preferred delivery strategy for multiple pregnancies is not abdominal delivery. The primary reasons for surgical delivery in multiple pregnancies are the same as in single pregnancies: ineffective labor

induction, loss of umbilical cord loops or small parts of the fetus, prior cesarean section, insufficient biological readiness of the birth canal, pregnancy following IVF-ET, and fetal distress. The preferred delivery strategy for multiple pregnancies is not abdominal delivery. The primary reasons for surgical delivery in multiple pregnancies are the same as in single pregnancies: ineffective labor induction, loss of umbilical cord loops or small parts of the fetus, prior cesarean section, the absence of biological readiness for childbirth, pregnancy following IVF-ET, and fetal distress.

In cases of multiple pregnancies, it is possible to uncover additional reasons for a cesarean section, including:

- prenatal amniotic fluid discharge and an unprepared birth canal;
- lack of sporadic labor activity, two hours after preterm amniotic fluid discharge;
- weakness of labor activity (uterine inertia);
- Intrauterine growth restriction (IUGR) II-III degrees, especially against the background of preeclampsia;
- premature birth with a fetal weight of less than 2 kg in the presence of a qualified neonatal service;
- fetal distress (or non-reassuring fetal status);
- The death of one fetus;
- monochorionic-monoamniotic twins;
- fetal macrosomia;
- transverse lie;
- breech presentation;
- conjoined twins;

multiple pregnancy (triplets or more).

## Discussion

The idea of performing cesarean sections while collecting children from the entire fetal membrane has recently been proposed. Due to this, resuscitation efforts for premature and immature neonates can be scaled back (27, 28). It is important to remember when managing the postpartum period that the processes of reverse development take longer in an expanded uterus than they would under normal circumstances. As a result, the uterus takes longer to contract and to empty, and postpartum uterine infections are more common. Women who have multiple pregnancies experience severe maternal morbidity and mortality due to the high frequency of pregnancy and birthing difficulties, which can be up to 3 to 7 times more common than single pregnancies (29). The body weight of the child has a direct correlation with perinatal mortality, which is 6–10 times more than with singleton pregnancy.

Monozygotic twins have a morbidity and mortality rate that is 2-3 times higher than dizygotic twins. Identical twins have a nearly 2-fold higher risk of prenatal death than fraternal twins. Prematurity births and intranatal complications are the most frequent causes of fetal mortality in multiple pregnancies (30-32).

With the advancements of modern neonatology, it is now possible to nurse fetuses whose gestational age is no greater than 23 weeks; nonetheless, this is accompanied by a high incidence, with intraventricular hemorrhages, chronic lung disorders, and necrotizing enterocolitis being the main reasons (33, 34).

Due to the high percentage of infants born at the same time that require primary resuscitation in serious conditions, it is advised to have two neonatologists in the delivery room in cases of multiple births (with triplets) (35-37). Blood transfusion to the donor fetus is one of the therapeutic options for treating FFTS after childbirth in order to restore the water-electrolyte balance. Venesection (phlebotomy) is carried out in the recipient fetus to bring venous pressure down to normal levels.

As a result, multiple pregnancies play an increasingly important role in population reproduction while also increasing the risk of reproductive losses due to the expansion of the use of reproductive technologies. The mother's body is put under additional, unique pressures when carrying many children. The presence of multiple pregnancies should be regarded as pathology, and such pregnant women should be carefully observed (particularly if they are carrying monochorionic twins).

## Conclusion

Preeclampsia and placental insufficiency are more likely to occur in multiple pregnancies than in single

pregnancies. As a result, starting at the beginning of the second trimester, all preventative measures should be implemented. Special attention should be paid to a diet high in protein, the use of iron supplements, and the intake of vitamins. It is recommended that women experiencing multiple pregnancies give birth in maternity facilities (perinatal centers) that are highly qualified and equipped with modern diagnostic and therapeutic equipment. This will allow for the provision of intensive care as well as specialized care to both the mother and the newborn. The birth technique is determined by the quantity of fetuses, how they appear, the gestational age, and the existence of gestational problems. Although abdominal delivery is not the preferred approach for multiple pregnancies, there are several situations where it may be necessary in the interest of the fetuses. Preventative measures for multiple pregnancies and deliveries should concentrate on strengthening organizational support for the maternity service and expanding access to high-quality medical care for this group of pregnant women.

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## Conflict of Interest

The authors declare no conflict of interest.

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