# COMPARING THE RISKS OF MULTIPLE PREGNANCIES WITH SINGLETON PREGNANCIES

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**Abstract:**

The prevalence of multiple pregnancies, driven by assisted reproductive techniques and delayed fertility age, has surged globally, prompting concerns about associated perinatal morbidity and mortality. In Turkey, the rise in multiple pregnancies led to regulatory measures in 2010, mandating single embryo transfer in assisted reproductive procedures, except for special cases. This paper explores the elevated risks in multiple pregnancies compared to singleton pregnancies, with a focus on perinatal outcomes such as preterm birth, hypertensive disorders, gestational diabetes mellitus, and bleeding complications during and after pregnancy.

The risks associated with multiple pregnancies intensify with the number of fetuses, leading to more severe complications. Adverse outcomes include low birth weight, early gestational age at birth, heightened rates of neonatal death, and increased neonatal intensive care unit admissions. To mitigate these risks and enhance maternal and fetal well-being, preconception counseling emphasizing the hazards of multiple pregnancies is crucial. Early diagnosis of multiple pregnancies, thorough evaluation of chorionic and amniotic membranes—especially for higher-risk monochorionic cases—and the establishment of personalized pregnancy monitoring plans are essential. Early intervention for potential complications during follow-up is imperative to minimize adverse outcomes.

**Keywords:** Multiple pregnancies, singleton pregnancies, perinatal morbidity, preterm birth, assisted reproductive techniques.

## Introduction:

The incidence of multiple pregnancies, the frequency of assisted reproductive techniques, and the global trend of increasing fertility age have risen in our country as well, as in the rest of the world. In Turkey, especially due to multiple pregnancies resulting from assisted reproductive techniques since the 1990s, perinatal morbidity and mortality, particularly associated with preterm birth, prompted the Ministry of Health to issue a regulatory directive on March 6, 2010. This directive, with exceptions for special cases, made the principle of single embryo transfer mandatory. Multiple pregnancies carry a higher risk of perinatal mortality and morbidity compared to singleton pregnancies, including preterm birth, hypertensive disorders, gestational diabetes mellitus, and increased risks such as bleeding during pregnancy and postpartum. These risks escalate with an increase in the number of fetuses, and complications aggravated by multiple pregnancies tend to be more severe.

Low birth weight, early gestational age at birth, increased rates of neonatal death, and admission to the neonatal intensive care unit are observed in babies born from multiple pregnancies.

To minimize maternal and fetal adverse outcomes, it is essential to provide preconception counseling on the risks of multiple pregnancies, diagnose multiple pregnancies as early as

possible, evaluate chorionic and amniotic membranes, particularly assessing the higher-risk monochorionicity, and establish a personalized pregnancy monitoring plan. Early intervention is crucial during follow-up for complications that may arise.

**The diagnosis of multiple pregnancies**

Monochorionic and dichorionic twin pregnancies can progress quite differently in terms of clinical outcomes; therefore, determining the chorionicity and amnionicity of multiple pregnancies at the earliest possible stage is crucial. Using transvaginal ultrasound (USG), the gestational sac and yolk sac can be visualized from the fifth week, and the embryo and heart activity can be clearly observed from the sixth week onwards. Zygosity denotes the type of conception, while chorionicity refers to placental formation.

The key point in diagnosis is the determination of chorionicity, which is possible through ultrasound imaging. The optimal time for chorionicity determination is after the seventh week in the first trimester (sensitivity ≥ 98%). In the early second trimester, chorionicity determination can also be performed with a lower but acceptable accuracy (sensitivity ≥ 90%).

After the 16th week, the chorion frondosum physiologically regresses, making it challenging to determine chorionicity.

**Maternal Physiology and Adaptation in Multiple Pregnancies**

In multiple pregnancies, there is an increase in normal pregnancy adaptations. Serum levels of progesterone, estradiol, estriol, hPL, hCG, and AFP are higher compared to singleton pregnancies. The increase in hPL contributes to gestational diabetes mellitus, while an increase in hCG enhances emesis. The cardiothoracic ratio and stroke volume increase, myocardial contractility and cardiac output rise, plasma volume expands, total fluid increases, colloid osmotic pressure decreases, edema tendencies emerge, and the risk of pulmonary edema rises. Dilutional anemia is more pronounced in multiple pregnancies than in singleton pregnancies. Daily calorie intake is increased from the recommended 2400 kcal/day in singleton pregnancies to 3000-4000 kcal/day in multiple pregnancies. Uterine volume grows rapidly, and by the 25th week, the size of the multiple pregnancy uterus is almost equivalent to that of a singleton pregnancy at term. Uterine blood flow increases, tidal volume and oxygen consumption rise, pH shifts towards alkalinity, and there is an increase in GFR and pressure in the renal collecting system. The changes mentioned above are more pronounced in triplet and quadruplet pregnancies.

**General Complications of Multiple Pregnancies**

Almost all complications seen in normal singleton pregnancies are more severe in multiple pregnancies, whereas macrosomia and post-term pregnancies are rarer.

1. Spontaneous abortion and vanishing twin
2. Congenital malformations
3. Low birth weight and preterm birth
4. Hypertension
5. Specific Fetal Complications

**Twin-to-Twin Transfusion Syndrome (TTTS)**

TTTS is a specific complication of monochorionic twin pregnancies and poses a vital risk for both babies. Almost all monochorionic twins have vascular connections resulting from placental anastomoses. TTTS complicates due to the shared placenta and interconnected vessels, leading to a decrease in perfusion in the donor twin and an increase in perfusion in the

recipient twin. Oligohydramnios and related intrauterine growth restriction (IUGR) develop in the donor twin, while polyhydramnios and associated intrauterine pressure increase, preterm labor, and preterm premature rupture of membranes (PPROM) may occur in the recipient twin.

TTTS can develop at any stage of pregnancy, with prognosis worsening the earlier it occurs. If left untreated, the risk of mortality is very high for both babies. After the death of one baby, the surviving baby faces a threat to their life due to the reversed blood flow, and without intervention, death becomes inevitable.

**Selective Intrauterine Growth Restriction** (sIUGR)

In monochorionic twin pregnancies sharing a single placenta poses risks for both fetuses. Unequal placental sharing can lead to selective intrauterine growth restriction (sIUGR), where one fetus experiences growth restriction compared to the other. This condition increases the risk of perinatal mortality and morbidity for the affected twin. sIUGR is observed in approximately 10% to 15% of monochorionic twin pregnancies. Diagnosis is made through ultrasound, comparing biometric measurements of both fetuses in the second trimester and detecting discordance. sIUGR is diagnosed when one fetus has an estimated fetal weight (EFW) below the 3rd percentile or meets two of the following criteria:

- One fetus has an EFW below the 10th percentile.
- One fetus has an abdominal circumference measurement below the 10th percentile.
- Umbilical artery pulsatility index (UA PI) >95th percentile for the smaller fetus.
- Weight discordance between the two fetuses exceeds 25%.

After the diagnosis based on umbilical artery Doppler findings, staging is crucial for follow-up and pregnancy management.

**Types of sIUGR based on umbilical artery Doppler findings:**

Type 1: Positive diastolic flow in the growth-restricted fetus. Type 2: Loss of end-diastolic flow and presence of reversed end-diastolic flow in the growth-restricted fetus. Type 3: Intermittent loss of end-diastolic flow and presence of reversed end-diastolic flow.

For Type 1, routine close monitoring is typically continued, and the prognosis is generally favorable. For Type 2 and Type 3, various approaches can be considered. One approach is to perform occlusive procedures for the IUGR twin, sacrificing the smaller twin to preserve the normal development of the other. Another approach involves using laser photocoagulation to separate the circulations between the twins physically, preserving the development of the normal twin in case of intrauterine death of the affected twin.

## GENERAL OBSTETRIC COMPLICATIONS

**Hypertensive Disorders:** Approximately 2-8% of pregnancies are complicated by hypertensive disorders (25). Risk factors for hypertensive disorders in pregnancy include age, family history, chronic diseases, multiple pregnancies, obesity, race, previous pregnancy complications, and thyroid problems.

**Gestational Hypertension:** It occurs after the 20th week of pregnancy, with a blood pressure measured at least twice, four hours apart, reaching 140/90 mmHg or higher without proteinuria. Severe preeclampsia is characterized by symptoms such as thrombocytopenia, renal failure, elevated liver enzymes, cerebral symptoms, and pulmonary edema.

**Preeclampsia, HELLP Syndrome, Eclampsia:** Preeclampsia is characterized by hypertension and proteinuria starting after the 20th week of pregnancy. Severe preeclampsia includes various symptoms along with high blood pressure. Eclampsia refers to generalized

seizures in a patient diagnosed with preeclampsia. HELLP syndrome involves hemolysis, elevated liver enzymes, and thrombocytopenia, often occurring within the spectrum of preeclampsia.

**Chronic Hypertension:** Chronic hypertension exists before pregnancy or occurs before the 20th week of gestation, lasting for more than 12 weeks postpartum.

**Preeclampsia on the Background of Chronic Hypertension:** In a chronically hypertensive pregnancy, worsening hypertension, newly onset proteinuria, and/or signs of end-organ damage after the 20th week of pregnancy lead to the diagnosis.

### Gestational and Pregestational Diabetes Mellitus

Diabetes during pregnancy is a common and complex condition that increases the risk of both fetal and maternal morbidity when complications arise. Pregestational diabetes diagnosed before pregnancy can be distinguished from gestational diabetes, which occurs during pregnancy. Screening for diabetes during pregnancy is crucial to prevent adverse outcomes, and appropriate treatment options should be provided.

**Risk Factors for Gestational Diabetes:**

- Impaired glucose tolerance in the medical history (HbA1c ≥ 5.7)
- Previous gestational diabetes (risk of recurrence in the next pregnancy is 40%)
- Family history of diabetes (especially in first-degree relatives)
- Pre-pregnancy BMI > 30 kg/m2 and excessive weight gain between 18-24 weeks of pregnancy
- Age 35 and older
- Ethnicity
- Conditions associated with insulin resistance (e.g., polycystic ovary syndrome)
- History of giving birth to a large baby (4000g and above)

Individuals with these risk factors should be screened for gestational diabetes early in pregnancy. Risks associated with gestational diabetes for both the mother and the baby include hypertensive disorders of pregnancy, macrosomic fetus leading to shoulder dystocia, risk of birth trauma for both mother and baby, operative delivery (vaginal and cesarean), fetal and/or neonatal hypertrophic cardiomyopathy, polyhydramnios, metabolic complications for the newborn (such as polycythemia, hypoglycemia, hyperbilirubinemia), perinatal mortality, and sudden infant death syndrome.

For individuals at high risk of gestational diabetes, lifestyle changes in the pre-pregnancy and early pregnancy periods can reduce risks. Lifestyle modifications such as weight loss, regular exercise, and smoking cessation can improve insulin resistance. While first-trimester diabetes screening is recommended for high-risk groups, for those without previous risk factors, gestational diabetes screening can be done between weeks 24 and 28 using a 50-gram glucose screening test, followed by diagnostic tests.

### Thromboembolic Diseases

Pregnancy, due to adaptive systems in its normal course, is a prothrombotic condition. Changes in hemostatic and thrombolytic balances favor thrombosis to control bleeding after placental separation during childbirth. Compared to non-pregnant women, pregnancy shows an increase in coagulation factors, a decrease in fibrinolysis, and an increase in platelet activation, all of which increase the risk of thrombosis and susceptibility to thromboembolic complications. The

two significant outcomes of this condition in pregnancy are Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), with arterial thrombosis being rare in pregnancy.

**Deep Vein Thrombosis**

DVT can occur isolated during pregnancy or a thrombus formed in the deep leg veins may detach and cause pulmonary embolism when it reaches the lungs. PE is one of the common causes of maternal deaths (9%). Therefore, determining the risk and applying prophylaxis during pregnancy is essential.

**Thromboembolic Diseases in Pregnancy**

Pregnancy, due to adaptive systems in its normal course, is a prothrombotic state. Disturbances in hemostatic and thrombolytic balances, shifting towards thrombosis, are preparations to control bleeding after placental separation during delivery. When compared to non-pregnant women, an increase in coagulation factors, a decrease in fibrinolysis, and an increase in platelet activation are observed in pregnancy. All these changes increase the risk of thrombosis and predispose to thromboembolic complications. The two major outcomes of this condition in pregnancy are Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), while arterial thrombosis is rare in pregnancy.

**Deep Vein Thrombosis (DVT)**

DVT in pregnancy can occur in isolation or a thrombus formed in the deep leg veins may dislodge and cause pulmonary embolism when it reaches the lungs. PE is a common cause of maternal deaths (9%). Therefore, identifying and applying prophylaxis for the risk in pregnancy is crucial.

Risk factors during pregnancy can be categorized into two periods: during pregnancy and in the postpartum period.

**Risk factors in the postpartum period:**

- Age over 35
- Hypertension, eclampsia, or preeclampsia
- Experience an infectious process after childbirth
- Stillbirth
- Operative delivery
- Complicated pregnancy with comorbid diseases
- BMI > 25 kg/m2
- Preterm birth
- Obstetric bleeding
- Smoking

Diagnosis of DVT in a complicated pregnancy: The diagnosis of DVT in pregnancy is made by demonstrating the inability to compress the proximal veins (femoral vein thrombosis) or showing poor flow in Doppler imaging of the femoral-iliac vein (iliac vein thrombosis) using compression ultrasound. The diagnosis is rarely confirmed by contrast or magnetic resonance venography, showing filling defects. D-dimer levels and clinical examination alone cannot be used to diagnose DVT.

**Pulmonary Embolism**

There is no clear symptom indicating pulmonary embolism in pregnancy, and it can be confused with dyspnea resulting from physiological changes during pregnancy. Therefore, diagnosing PE is challenging, but it should be thoroughly investigated due to its life-threatening nature. Arterial blood gas analysis, D-dimer levels, and echocardiography are often performed, but their sensitivity for diagnosis is not very high. Without confirmatory imaging, the diagnosis of embolism is not definitive. The two most commonly used imaging methods are lung scintigraphy (ventilation/perfusion scan [V/Q]) and computed tomographic pulmonary angiography (CTPA). In pregnant women presenting with symptoms of PE, compression ultrasound for detecting DVT should be performed, and a chest X-ray should be taken. After these, lung scintigraphy and CTPA should be performed. The decision to use radiation and contrast exposure to the fetus should be based on the risk-benefit ratio to recognize a potentially fatal condition for the mother.

**Treatment of VTE in Pregnancy:** VTE treatment in pregnancy relies on the use of anticoagulants. The management of suspected VTE depends on the degree of clinical suspicion for acute PE, the presence of contraindications for anticoagulation, and whether suspicion involves PE, DVT, or both.

- In cases of high clinical suspicion of acute PE, empirical anticoagulant treatment is indicated before confirmation of the diagnosis. If VTE is ruled out, the treatment is discontinued.
- In cases of moderate or low suspicion of PE, the decision to start anticoagulant treatment before diagnostic evaluation is based on individual patient assessment.
- If PE is suspected but anticoagulant treatment is contraindicated, the diagnosis should be established as soon as possible, and alternative methods (e.g., inferior vena cava filter) should be considered.
- In cases of isolated DVT suspicion without evidence of PE or VTE, anticoagulant treatment is initiated when DVT is confirmed.

**Kidney and Urinary System Pathologies**

Adaptations in the kidneys and urinary system during pregnancy result in kidney enlargement, dilated ureters, increased glomerular filtration rate (GFR) and renal plasma flow, decreased bicarbonate due to progesterone stimulation of respiration, and a tendency towards respiratory acidosis. All these lead to changes in the structure and function of the urinary system.

Pathologies observed in the kidneys and urinary system during pregnancy include:

- Urinary system infections: Bacterial infections generally originating from perineal flora are common in pregnancy. Asymptomatic bacteriuria and complicated urinary tract infections such as cystitis and pyelonephritis may occur.
- Nephrolithiasis: While calcium oxalate stones are common in non-pregnant young women, calcium phosphate and hydroxyapatite stones are common in pregnancy.
- Glomerular diseases
- Preeclamptic kidney damage
- Acute kidney injury
- Pathologies due to pressure from the growing uterus

Endocrine Pathologies Thyroid diseases: During a normal pregnancy, there are changes in thyroid function to meet the increased metabolic demand. There is an increase in serum thyroxine-binding globulin, and TSH receptors are stimulated by bHCG. Temporary

subclinical hyperthyroidism is considered a normal physiological condition. In the later stages of pregnancy, hCG decreases, T3-T4 levels decrease, and TSH returns to the normal range. Hyperthyroidism and hypothyroidism increase the risk of morbidity for both the mother and the fetus during pregnancy, so early detection and intervention are essential in the early stages of pregnancy. Parathyroid diseases: Parathyroid hormone maintains serum calcium balance, and maternal serum calcium levels should remain balanced for both the mother and the baby during pregnancy. Hyperparathyroidism during pregnancy is often associated with a parathyroid adenoma. Surgical intervention may be considered if it becomes symptomatic. Adrenal gland diseases: These are generally pre-existing conditions before pregnancy. Conditions include pheochromocytoma, Cushing's syndrome, Addison's disease (adrenal insufficiency), and hyperaldosteronism. Pituitary gland diseases: During pregnancy, pituitary enlargement may occur due to lactotroph cell hyperplasia induced by estrogen. In addition to physiological changes, pre-existing diseases can complicate pregnancy. Prolactinoma, acromegaly, Sheehan syndrome, and pituitary-related pathologies can occur both before and during pregnancy.

Obstetric Hemorrhage Vaginal bleeding is common in almost every trimester of pregnancy, and the approach varies depending on the trimester and the nature of the bleeding.

Hemorrhages Occurring During Pregnancy First-trimester bleeding: This is the period when bleeding is most common, evaluated until 13 weeks + 6 days. Main causes include ectopic pregnancy, early pregnancy loss, threatened miscarriage, physiological bleeding due to implantation, and vaginal-cervical-uterine pathologies. Transvaginal ultrasound is generally sufficient for diagnosis. Ectopic pregnancy rupture should be ruled out as it can cause life-threatening bleeding. Second and third-trimester bleeding: It is less common than in the first trimester, and the risk of pregnancy loss is higher than in the early period. Major causes include cervical insufficiency or dilation, placenta previa, placental abruption, pregnancy loss, uterine rupture, and vasa previa.

In conclusion, we emphasize that preventing iatrogenic multiple pregnancies by advocating for the transfer of a single embryo even in repeated procedures can reduce both maternal and perinatal complications. This is due to the more frequent and severe adverse outcomes associated with multiple pregnancies compared to singleton pregnancies, and the lack of demonstrated improvement in pregnancy outcomes through treatment procedures in perinatal centers.

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