Preeclampsia in twin pregnancy
Pré-eclâmpsia na gravidez gemelar

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Abstract

Twin pregnancy is a high-risk condition and its incidence has raised over the last decades. Hypertensive disorders are among the most common medical complications of pregnancy. While is unquestionable that multiple pregnancy has an increased risk of preeclampsia (PE), it's unclear what are the other risk factors.
The pathophysiology of PE is uncertain but is thought to be a condition of poor placentation, resulting in generalized vascular endothelial activation and vasospasm.
Published data also show that an angiogenic/anti-angiogenic balance plays a causative role in endothelial cell injury.
Increasing the knowledge about PE in twin gestation may improve patient's surveillance.

Keywords: Twin pregnancy; Preeclampsia

INTRODUCTION

Currently, with the increase in maternal age and the expanding use of assisted reproductive technology (ART), obstetricians have to deal with a growing number of multiple pregnancies, which differ from singleton in terms of monitoring, complications and outcomes[1-4].

Overall, twins' gestations constitute 2% to 5% of all pregnancies and they have an increased risk of almost all pregnancy complications, with preeclampsia (PE) being one of the most significant[1,3,5].

PE is a pregnancy-specific hypertensive disorder, progressive and multi-systemic. There are several aspects of PE that are not fully understood, given rise to different definitions, diagnostic criteria and guidelines among the main scientific societies[6-11].

The early identification of twin pregnancies with a greater risk of PE would allow a tailored antenatal care and the possibility to introduce prophylactic measures to potentially reduce its incidence[12-14].

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DEFINITION

The most commonly used definition of PE is from the International Society for the Study of Hypertension in Pregnancy (ISSHP): development of hypertension (blood pressure equal or higher than 140/90 mmHg on two separate occasions, four hours apart after 20 weeks of gestation) in previously normotensive women with the presence of proteinuria (300mg or more in 24 hours or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens)[7].

In 2014, the definition was adjusted by the ISSPH[8], further to which the diagnosis of PE should be made in the presence of *de novo* hypertension after 20 weeks of gestation and new onset of one or more of the following criteria:

- proteinuria (≥300 mg/day or a spot urine protein/ /creatinine ratio ≥30 mg/mmol);
- renal insufficiency (creatinine ≥90 mmol/L);
- liver involvement (elevated transaminases and/or severe right upper quadrant or epigastric pain);
- neurological involvement (hyperreflexia accompanied by clonus, severe headaches accompanied by hyperreflexia, persistent visual scotomata, eclampsia, altered mental status, blindness, stroke);
- haematological complications (thrombocytopenia, haemolysis, Disseminated Intravascular Coagulation);

- uteroplacental dysfunction - fetal growth restriction.

These clinical manifestations result from mild to severe microangiopathy of the respective organs and should resolve completely within 12 weeks postpartum[8].

In terms of gestational age, PE can be classified as early-onset PE when the diagnosis is made at or before 34 weeks gestation. PE is defined as preterm or term, according to the need for iatrogenic delivery before or after 37 weeks of gestation, respectively[15].

INCIDENCE

PE complicates 4 to 5% of pregnancies worldwide and its incidence has increased by 25% in the past two decades[16-21]. Twin pregnancies have an increased risk of hypertensive diseases, with reported rates varying from 13 to 36%[3,5,22]. This fact was first noted by Hinselmann on the 18th century. Of the 7748 cases of eclampsia recorded in his work, 6,4% were in twin pregnancies, a rate 5,8 times higher than in singletons.[5] During the last 20 years numerous studies compared single and multiple pregnancy in terms of rate of gestational hypertension, PE and eclampsia. According to those reports, the relative risk of gestational hypertension is 1.2 to 2.7, for PE is 2.8 to 4.4 and for eclampsia 3.4 to 5.1, when comparing twin to singleton gestations[23,24].

Traditionally, the relative risk described for PE in twins is 3. However, if we consider that the gestational age at delivery in multiples is lower than in singletons, is logical to assume that the real relative risk of PE in twins is underestimate. If we compare the rate of preterm-PE in multiple with singleton pregnancies, the rate is actually 9-times higher. Indeed, the relative risk for preterm-PE in the subgroup of pregnancies that are ongoing at 35 weeks' gestation is 14 for dichorionic (DC) and 20 for (MC) monochorionic twins[25]. Therefore, PE in multiple gestation is a rather pertinent problem in obstetric practice.

RISK FACTORS

Throughout the years multiple factors have been identified as potentially increasing the incidence and severity of hypertensive disorders in singleton pregnancies. The most important are nulliparity, advanced maternal age (AMA), black race, obesity, ART, gestational diabetes and antiphospholipid antibodies[6].

Although it can be presumed that the risk factors for PE in multiple pregnancies are the same, due to the difference in maternal and pregnancy characteristics, this hypothesis is unproven. Data are limited, contradictory and most of the published studies have important bias, limiting the strength of the evidence available[26].

Parity

Similar to singleton pregnancies, parity appears to have a significant impact in the development of PE in multiple gestations. According to the literature, nulliparity increases the relative risk of PE approximately 3 times (1.6-5.2) in twin pregnancy. Additionally, the combination of nulliparity with a twin pregnancy increases the risk of PE around 14 times, when compared to a multiparous with a singleton pregnancy[5,22,26].

Age

When analyzing maternal age, the risk of PE has a U-type distribution, being the lowest between 25 and 29 years and the highest in the group over 40 years. Young mothers (<17 years of age) with twin pregnancies are at a relative risk 1.5 times higher for developing PE compared to those aged 17 to 25, and at an even higher risk compared to those older than 25 years[5].

Race

In twin pregnancies, race seems to play a less important role than in singletons, with black mothers having only a 1.8 times higher risk of PE than white mothers[5].

Pregestational Body Mass Index

Some studies showed that a higher pregestational Body Mass Index (BMI), especially a BMI superior to 30 kg/m^2, increases significantly and independently the risk of PE in twins[26,27].

Previous history of hypertensive disorder in pregnancy

As in singleton pregnancies, a past history of preeclampsia increases significantly the risk of developing PE, when compared with women without this background[27].

Zygosity

The results of studies on the importance of zygosity are inconsistent, with rates of PE in monozigotic reported as higher, similar or lower compared to dizigotic twin pregnancies[28]. These contradictory results

may be due to the changing definitions of PE over time, as well as to the determination of zygosity. The only accurate way to determine zygosity is analysing DNA markers, which can only be done prenatally by invasive testing. From a clinical point of view, the determination of zygosity is not easily available and it does not have the potential to be used as an element in screening large populations[29,30].

Chorionicity

Much more important than zygosity is chorionicity that can be reliably determined in the first trimester by ultrasonography. The association between PE and chorionicity is unclear and the existing data are incongruous. There are studies showing a higher risk in DC twins[31-33], others a lower risk of PE[34] and some concluding lack of association[28,35,36].

These incongruent findings can be explained by inconsistent diagnoses of PE, small sample sizes and lack of adjusting data to possible confounding factors. One important bias is the gestational age at delivery, as there is a higher rate of preterm delivery in MC twins. Another important confounder is maternal age: DC twins are more frequent in older mother. More recent studies using multiple logistic regression, revealed that chorionicity has no effect on the development of PE after adjusting for confounding factors like maternal age, race, parity and gestational age at delivery[26,27,29].

Assisted Reproductive Technology

ART role in the incidence of PE in multiple gestations has been explored in several studies with controversial findings. Some authors found an increased risk of PE in ART pregnancies[37,38], while others found no difference between ART and spontaneous twins gestations[35,39,40].

Similar to what happens with chorionicity, these contrasting findings can be related to sample sizes and possible confounding factors. When using a multiple logistic regression model the use of ART by itself seems to have no influence in the risk of PE. Nevertheless, some particularities of the technique used, such as egg donation, seem to increase the rate of PE[26,39,40].

Other factors

Gestational diabetes, family history of hypertension, maternal smoking, income level and genetic factors apparently have little or no effect on the development of PE in twins[5,22,27].

The latest studies support that the only risk factors independently associated with PE in twin pregnancy are pregestational high BMI, egg donation, previous history of hypertensive disorder in pregnancy and probably nulliparity[22,26]. Additional studies are needed to confirm these findings.

PATHOPHYSIOLOGY

The pathophysiology of PE is still poorly understood but it is likely to involve both maternal and placental factors. Abnormalities in the development of placental vasculature in early pregnancy may cause placental hypoxia and the release of factors leading to maternal endothelial dysfunction, triggering hypertension and other disease manifestation. The different theories on the pathogenesis of PE in singletons can be extrapolated for twin pregnancy.

Imunological factors

The immune incompatibility theory supports that the immunological/genetic differences between mother and fetus contribute to the development of PE. This theory states that an immunologic event early in pregnancy activates a maladaptation of the maternal immune system to the fetal trophoblastic tissue[41].

Various studies have proved the existence of increased levels of fetal nucleic acids and syncytiotrophoblast microparticles in maternal blood among women with PE. If the immunological load is determinant in the development of PE, the incidence of PE should be higher in dizygotic twins and similar in monozygotic twins and singleton pregnancies. Given most of the DC are dizygotic it would be expected that the incidence of PE to be higher in DC compared to MC twins. The newest studies have however demonstrated similar incidences in both types of twins, which does not support the immunological concept[28,29,33,42].

Placentation

One key element involved in PE is placentation. An impaired trophoblastic invasion of maternal spiral arteries can lead to a high-pressure flow and damage to the placenta, resulting in placental hypoxia and release of factors leading to maternal endothelial dysfunction[12,43,44].

One possible explanation for the increased rate of PE among women with twin gestations is the placental mass hypothesis. Twins have a larger placental mass, which may cause an increased release of molecules with anti-angiogenic activity, like soluble fms-like tyrosine

kinase-1 (sFlt-1) and soluble endoglin (sEng). However, some studies found no correlation between placental mass and circulation levels of anti-angiogenic factors, making the placental mass hypothesis unlikely[33,34,45,46].

Another possible justification for the increased risk of PE in multiple pregnancy is the existence of a less efficient placentation. In twins is more likely that at least one placenta is implanted in a hostile part of the uterus, potential resulting in some degree of hypo-perfusion. It is undoubted that the anti-angiogenic factors have a vasoconstrictor role and induce placental ischemia/hypoxia, but it is still not clear whether placental hypoxia is the effect or the cause of increased anti-angiogenic factors release[30,45].

Angiogenic factors

The angiogenic/angiostatic balance theory supports that there is a variation in the balance of angiogenic proteins, inflammatory cytokines and other immune-modulating molecules in pregnancies with PE. These factors are thought to cause maternal endothelial dysfunction and a systemic inflammatory reaction[41].

Numerous studies in singletons showed an elevation in sFlt-1 and sEng, two anti-angiogenic proteins, previously to the clinical manifestation of PE. Placental growth factor (PlGF) is a protein mainly expressed in the placenta and is considered to be an angiogenic factor. The circulating levels of PlGF decrease before the onset of PE and an increased of the sFlt-1/PlGF ratio has also been shown to precede the clinical symptoms of PE[12].

When comparing unaffected singleton and twin pregnancies, studies demonstrated higher levels of sFlt-1 and higher sFlt-1/PlGF ratio in twins. When comparing twins with PE *versus* unaffected twin pregnancies, the serum levels of sFlt-1 and the sFlt-1/PlGF-ratio are significantly increased and PlGF is significantly decreased. The deviations of these angiogenic markers appear to predict adverse outcomes, and the sFlt-1/PlGF-ratio is inversed correlated with the duration of pregnancy[45-49].

These findings support the hypothesis that the angiogenic/angiostatic balance plays a relevant role in endothelial cell injury, in multiple as in singleton pregnancies. Although the placenta is central to the process, it remains unclear what causes sFlt-1 to increase and PlGF to decrease in women with PE, but it probably points to the multifactorial aspect of this disease.

Cardiovascular theory

Despite the fundamental role of the cardiovascular system in PE, data about the interaction between the placenta and the maternal heart are still limited.

It has been proposed that numerous cases of PE can be related to failure of the maternal heart muscle to remodel, especially in relation to diastolic blood pressure. Recent studies consistently show that women with placental failure and impaired left ventricle function were more likely to develop early-onset PE. These results originated the theory that the maternal cardiovascular response to placental dysfunction may play an important role in the pathophysiology of PE. These cardiac changes may also play a part in the increased pre-disposition of women with PE to develop long-term cardiovascular disease[15,50].

In twin pregnancy complicated by PE it is recognized that the maternal cardiac function does not undergo the physiological changes that are required for adaptation to pregnancy. As in singletons, a failure in maternal cardiac adaptation, demonstrated by a lower cardiac output and increased total vascular resistance, has been associated with an increased risk of PE[51].

The latest evidence suggests that the most significant factors in the pathophysiology of PE in twin pregnancy, as in singletons, are related to the angiogenic balance and the maternal cardiovascular response to placental dysfunction. Further investigation focused on multiple pregnancies is essential to validate theses conclusions.

CLINICAL MANIFESTATIONS

The clinical manifestations of PE appeared to be similar in singleton and twins. However, hypertensive disorders in multiple pregnancies tend to occur earlier and to be more severe.

Preterm PE occurs 2,8 to 3,7 times more frequently than in singleton pregnancies. This results in a higher probability of complications such as preterm delivery, 34,5% in twin gestation versus 6,3% in singletons[5,23,43,52].

Twin pregnancies also have an increased risk (about 3 times higher) of eclampsia. *Abruptio placentae* was found to be 8,2 times more frequent in twin pregnancies with PE when compared to singletons and 5,4 times when compared to normotensive twin pregnancies[5,22,43,53,54].

The diagnosis and management of PE are similar to those in singleton pregnancies[1].

SCREENING

The early detection of pregnancies at high-risk of developing PE may improve the maternal and neonatal outcomes by allowing a more intensive and personalised surveillance and the use of prophylactic measures[55,56].

In singleton pregnancies, screening for PE in the first trimester using a multifactor approach, combining maternal characteristics, biophysical and biochemistry markers, has a detection rate for early PE of 93.4% for a 5% false-positive rate[57].

In twin pregnancies, PE screening data are scarce. Several studies have assessed the potential impact in multiple pregnancies of the factors traditionally used for screening in singletons[44,45,58,59].

The distribution of mean arterial pressure (MAP) values in unaffected pregnancies was similar in twin and singleton pregnancies. Additionally, in twins with PE the levels of MAP were elevated parallel to what happens in singletons with PE[59].

Studies have proven that the mean uterine artery pulsatility index (UtA-PI) is lower in twins than in singletons. In twin pregnancies, UtA-PI is increased in the first trimester in pregnancies that develop early-onset PE but not significantly in the cases of late-onset PE. These findings are consistent with those found in singleton pregnancies, showing that uterine artery Doppler is more efficient in identifying women who develop severe early-onset PE rather than the late form of the disease[44,60,59].

In twins with PE *versus* unaffected pregnancies, the serum levels of sFlt-1 and the sFlt-1/PlGF-ratio are significantly increased and PlGF is significantly decreased. These results are comparable to those found in singleton pregnancy[45,46,48,58].

Similarly to what happens in singletons, the best performance of screening for PE in twin pregnancies should be achieved with a combined model. Studies specifically aiming to screen for PE in multiple pregnancies are required.

PREVENTION

In singletons pregnancies several strategies to prevent PE have been studied, but only the use of low-dose dose aspirin has been found to be effective[57,61]. If screening is carried out before 16 weeks of pregnancy, the daily administration of a low-dose dose aspirin in the high-risk patient reduces in 10 times the incidence of early-onset PE[62,63].

There is little data about the use of aspirin in multiple pregnancies[64,65]. There are some health organizations that support the routine use of low-dose aspirin in all twin pregnancies to prevent PE[66,67]. Nonetheless, if the adverse effects and compliance are considered, possibly not every twin pregnancy should receive aspirin. Screening strategies intended to select higher-risk twin pregnancies would be preferable to indiscriminate use.

CONCLUSION

PE is among the most common complications in pregnancy, representing a major cause of maternal and perinatal mortality and morbidity. However, its physiopathology is still poorly understood, which generates several unanswered questions. Nowadays, obstetricians face a growing number of multiple pregnancies, which have an increased risk of PE.

The maternal risk factors for PE in twins appear to be somewhat different from singleton pregnancy, although the available data are inconsistent and larger studies are necessary.

The pathophysiology of PE in twins, as in singleton pregnancies, is related to an impaired utero-placental circulation combined with abnormal anti-angiogenic balance and a maternal cardiac maladaptation. Given the particularities of PE in twins, research focused to multiple pregnancy is needed.

Further investigation is fundamental to clarify if there is any effective prophylactic measure in twin pregnancy and if it is more cost-effective to screen these pregnancies or to offer prophylactic measures universally. If screening is the way forward, it is imperative to determine what is the best screening method.

Considering all this questions, PE in twin pregnancies is a pertinent obstetric problem of increasing importance, requiring more research to elucidate the particularities of this pathology.

REFERENCES

1. Chasen S, Chervenak F. Twin pregnancy: Prenatal issues. [Online].; 2017 [cited 2017. Available from: www.uptodate.com

2. Fletcher B. Multiple Births. [Online].; 2015 [cited 2017 October. Available from: https://emedicine.medscape.com

3. American College of Obstetricians and Gynecologists; Society for Maternal-Fetal Medicine. ACOG Practice Bulletin No. 169: Multifetal gestations: twin, triplet, and higher-order multifetal preg-

nancies. Obstet Gynecol. 2016 October; 128: p. e131–46.

4. Ananth C, Chauhan S. Epidemiology of twinning in developed countries. Semin Perinatol. 2012 Jun; 36(3): p. 156-161.

5. Krotz S, Fajardo J, Ghandi S, Patel A, Keith L. Hypertensive Disease in Twin Pregnancies: A Review. Twin Research. 2002; 5(1): p. 8-14.

6. August P, Sibai B. Preeclampsia: Clinical features and diagnosis. [Online].; 2017 [cited 2017 October. Available from: www.uptodate.com

7. Brown M, Lindheimer M, Swiet M, Assche A, Moutquin J. The Classification and Diagnosis of the Hypertensive Disorders of Pregnancy: Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertension in Pregnancy. 2001; 20(1).

8. Tranquilli A, Dekker G, Magee L, Roberts J, Sibai B, Steyn W. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2014; 4: p. 97-104.

9. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013; 122(5): p. 1122-1131.

10. National Collaborating Centre for Women's and Children's Health (UK). Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. National Institute for Health and Clinical Excellence: Guidance. 2010.

11. Society of Obstetric Medicine of Australia and New Zealand. Guidelines for the management of hypertensive disorders of pregnancy 2014. Aust N Z J Obstet Gynaecol. 2015; 55: p. 11-16.

12. Ohkuchi A, Hirashima C, Takahashi K, Suzuki H, Matsubara S. Prediction and prevention of hypertensive disorders of pregnancy. Hypertens Res. 2017; 40(1): p. 5-14.

13. Euser A, Metz T, Allshouse A, Heyborne K. Low-dose aspirin for pre-eclampsia prevention in twins with elevated human chorionic gonadotropin. J Perinatol. 2016; 36(8): p. 601–605.

14. Maymon R, Trahtenherts A, Svirsky R, Melcer Y, Madar-Shapiro L, Klog E, et al. Developing a new algorithm for first and second trimester preeclampsia screening in twin pregnancies. Hypertens Pregnancy. 2017; 36(1): p. 108-115.

15. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular Implications in Preeclampsia An Overview. Circulation. 2014; 130(8): p. 703-714.

16. Sibai B. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol. 2003; 102: p. 181–192.

17. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000; 183: p. S1– S22.

18. Abalos E, Cuesta C, Grosso A. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;: p. 170- 171.

19. Hutcheon J, Lisonkova S, Joseph K. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2011; 25: p. 391-403.

20. Ananth C, Keyes K, Wapner R. Pre-eclampsia rates in the United States, 1980- 2010: age-period-cohort analysis. BMJ. 2013; 347: p. 6564 - 6569.

21. Lisonkova S, Sabr Y, Mayer C. Maternal morbidity associated with early-onset and late- onset preeclampsia. Obstet Gynecol. 2014; 124: p. 771-780.

22. Taguchi T, Ishii K, Hayashi S, Mabuchi A, Murata M, Mitsuda N. Clinical features and prenatal risk factors for hypertensive disorders in twin pregnancies. J Obstet Gynaecol. 2014; 40(6): p. 1584–1591.

23. Sibai B, Hauth J, Caritis S, Lindheimer M, MacPherson C, Klebanoff M. Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol. 2000; 182: p. 938–942.

24. Duckitt K, Harrington D. Risk factors for preeclampsia at antenatal booking: Systematic review of controlled studies. British Medical Journal. 2005; 330: p. 565-571.

25. Francisco C, Wright D, Benko Z, Syngelaki A, Nicolaides K. Hidden high rate of pre-eclampsia in twin compared with singleton pregnancy. Ultrasound Obstet Gynecol. 2017; 50: p. 88-92.

26. Fox N, Roman A, Saltzman D, Hourizadeh T, Hastings J, Rebarber A. Risk factors for preeclampsia in twin pregnancies. Am J Perinatol. 2014; 31(2): p. 163-166.

27. Lucovnik M, Tul N, Verdenik I, Novak Z, Blickstein I. Risk factors for preeclampsia in twin pregnancies: a population-based matched case-control study. J Perinat Med. 2012; 40: p. 379–382.

28. Savvidou M, Karanastasi E, Skentou C, Geerts L, Nicolaides K. Twin chorionicity and pre-eclampsia. Ultrasound Obstet Gynecol. 2001; 18(3): p. 228-231.

29. Singh A, Singh A, Surapaneni T, Nirmalan P. Pre-eclampsia (PE) and Chorionicity in Women with Twin Gestations. J Clin Diagn Res. 2014; 8(1): p. 100 - 102.

30. Sebire N. Routine uterine artery Doppler screening in twin pregnancies?. Ultrasound Obstet Gynecol. 2002; 20: p. 532-534.

31. Bartnik P, Kosinska-Kaczynska K, Kacperczyk J, Ananicz W, Sierocinska A, Wielgos M, et al. Twin Chorionicity and the Risk of Hypertensive Disorders: Gestational Hypertension and Pre-eclampsia. Twin Res Hum Genet. 2016 Aug; 19(4): p. 377-382.

32. Sarno L, Maruotti G, Donadono V, Saccone G, P M. Risk of preeclampsia: comparison between dichorionic and monochorionic twin pregnancies. Matern Fetal Neonatal Med. 2014; 27(10): p. 1080–1081.

33. Sparks T, Cheng Y, Phan N, Caughey A. Does risk of preeclampsia differ by twin chorionicity? J Matern Fetal Neonatal Med. 2013; 26(13): p. 1273-1277.

34. Campbell D, Templeton A. (2004) Maternal complications of twin pregnancy. Int J Gynaecol Obstet. 2004; 84(1): p. 71-73.

35. Suzuki S, Igarashi M. Risk factors for preeclampsia in Japanese twin pregnancies: comparison with those in singleton pregnancies. Arch Gynecol Obstet. 2009; 280: p. 389–393.

36. Carter E, Bishop K, Goetzinger K, Tuuli M, Cahill A. The impact of chorionicity on maternal pregnancy outcomes. Am J Obstet Gynecol. 2015; 213(3): p. 390.e1-7.

37. Pourali L, Ayati J, Zarifian A. Obstetrics and perinatal outcomes of dichorionic twin pregnancy following ART compared with spontaneous pregnancy. Int J Reprod BioMed. 2016 May; 14(5): p. 317-322.

38. Chaveeva P, Carbone I, Syngelaki A, Akolekar R, Nicolaides K. Contribution of Method of Conception on Pregnancy Outcome after the 11–13 Weeks Scan. Fetal Diagn Ther. 2011; 30(1): 9-22.

39. Fan C, Sun Y, Yang J, Ye J, Wang S. Maternal and neonatal outcomes in dichorionic twin pregnancies following IVF treatment: a hospital-based comparative study. Int J Clin Exp Pathol. 2013; 6: p. 2199-2207.

40. Anbazhagan A, Hunter A, Breathnach F, Mcauliffe F, Geary M, Daly S. Comparison of outcomes of twins conceived spontaneously and by artificial reproductive therapy. J Matern Fetal Neonatal Med. 2014; 27: p. 458-462.

41. Karumanchi S, Lim K, August P. Preeclampsia: Pathogenesis. [Online].; 2017 [cited 2017 October. Available from: www.uptodate.com

42. Maxwell C, Lieberman E, Norton M, Cohen A, Seely H, Lee-Parritz A. Relationship of twin zygosity and risk of preeclampsia. Am J Obstet Gynecol. 2001 Oct;185(4):819-21. 2001 Oct; 185(4): p. 819-821.

43. Weiner E, Feldstein O, Schreiber L, Grinstein E, Barber E, Dekalo A, Bar J, Kovo M. Placental Component and Pregnancy Outcome in Singleton versus Twin Pregnancies Complicated by Preeclampsia. Fetal Diagn Ther. 2018; 44(2):142-148.

44. Rizzo G, Pietrolucci M, Aiello E, Capponi A, Arduini D. Uterine artery Doppler evaluation in twin pregnancies at 11+0 to 13+6weeks of gestation. Ultrasound Obstet Gynecol. 2014; 44(5): p. 557 - 561.

45. Fauple-Badger Jea. Maternal Circulating Angiogenic Factors in Twin and Singleton Pregnancies. Am J Obstet Gynecol. 2015; 212(5): p. 636.e1–636.e8.

46. Dröge L, Herraìz I, Zeisler H, Schlembach D, Stepan H, Küssel L, et al. Maternal serum sFlt-1/PlGF ratio in twin pregnancies with and without pre-eclampsia in comparison with singleton pregnancies. Ultrasound Obstet Gynecol. 2015; 45(3): p. 286-293.

47. Bdolah Y, Lam C, Rajakumar A, Shivalingappa V, Mutter W, Sachs B. Twin Pregnancy and the Risk of Preeclampsia: Bigger Placenta or Relative Ischemia? Am J Obstet Gynecol. 2008; 198(4): p. 428.e1–428.e6.

48. Rana S, Hacker M, Modest A, Salahuddin S, Lim K, Verlohren S, et al. Circulating angiogenic factors and risk of adverse maternal and perinatal outcomes in twin pregnancies with suspected preeclampsia. Hypertension. 2012; 60(2): p. 451-458.

49. Francisco C, Wright D, Benk Z, Syngelaki A, Nicolaides K. Competing-risks model in screening for pre-eclampsia in twin pregnancy according to maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol. 2017 Nov; 50(5): p. 589--595.

50. Osol G, Bernstein I. Preeclampsia and Maternal Cardiovascular Disease: Consequence or Predisposition?. J Vasc Res. 2014; 51(4): p. 290-304.

51. Ghi T, Kuleva M, Youssef A, Maroni E, Nanni M, Pilu G, et al. Maternal cardiac function in complicated twin pregnancy: a longitudinal study. Ultrasound Obstet Gynecol. 2011; 38: p. 581–585.

52. Yuan T, Wang W, Li X, Li C, Li C, Gou W, et al. Clinical characteristics of fetal and neonatal outcomes in twin pregnancy with preeclampsia in a retrospective case–control study: A STROBE-compliant article. Medicine (Baltimore). 2016; 95(43): p. e5199.

53. Henry D, McElrath T, Smith N. Preterm severe preeclampsia in singleton and twin pregnancies. Journal of Perinatology. 2013; 33: p. 94–97.

54. Svirsky R, Meiri H, Herzog A, Kivity V, Cuckle H, Maymon R. First trimester maternal serum placental protein 13 levels in singleton vs. twin pregnancies with and without severe pre-eclampsia. J Perinat Med. 2013; 41(5): p. 561-566.

55. Poon L, Kametas N, Maiz N, Akolekar R, Nicolaides K. First-trimester prediction of hypertensive disorders in pregnancy. Hypertension. 2009; 53: p. 812–818.

56. American College of Obstetricians and Gynecologists. First-trimester risk assessment for early-onset preeclampsia. Committee Opinion No. 638. Obstet Gynecol. 2015; 126: p. 25-27.

57. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides K. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Fetal Diagn Ther. 2013; 33: p. 8-15.

58. Svirsky R, LTO, Feldman N, Klog ECH, Maymon R. First- and second-trimester maternal serum markers of pre-eclampsia in twin pregnancy. Ultrasound Obstet Gynecol. 2016; 47: p. 560–564.

59. Svirsky R, Yagel S, Ben-Ami I, Cuckle H, Klug E, Maymon R. First trimester markers of preeclampsia in twins: maternal mean arterial pressure and uterine artery Doppler pulsatility index. Prenat Diagn. 2014; 34(10): p. 956-960.

60. Geipel A, Hennemann F, Fimmers R, Willruth A, Lato K, Gembruch U. Reference ranges for Doppler assessment of uterine artery resistance and pulsatility indices in dichorionic twin pregnancies. Ultrasound Obstet Gynecol. 2011; 37: p. 663–667.

61. Norwitz ER. Early pregnancy prediction of preeclampsia. [Online].; 2017 [cited 2017 June. Available from: www.uptodate.com

62. Roberge S, Villa P, Nicolaides K, Giguère Y, Vainio M, Bakthi A, Ebrashy A, Bujold E. Early administration of low dose aspirin for the prevention of preterm and term pre-eclampsia: a systematic review and meta-analysis. Fetal Diagn Ther. 2012;31: p. 141--146.

63. Rolnik D et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. 2017; 337(7): p. 613--622.

64. Caspi E, Raziel A, Sherman D, Ariel S, Bukovski I, Weinraub Z. Prevention of pregnancy-induced hypertension in twins by early administration of low-dose aspirin: a preliminary report. Am J Reprod Immunol. 1994; 31 (1): p. 19-24.

65. Euser A, Metz T, Allshouse A, Heyborne K. Low-dose aspirin for pre-eclampsia prevention in twins with elevated human chorionic gonadotropin. J Perinatol,. 2016; 36(8): p. 601–605.

66. World Health Organization. WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia. 2011.

67. U.S. Preventative Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161: p. 819–826.

67. August P. Preeclampsia: Prevention. [Online].; 2017 [cited 2017 June. Available from: www.uptodate.com

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