

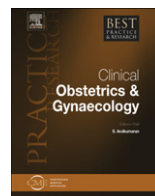


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A guide towards pre-pregnancy management of defective implantation and placentation

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Pregnancy complications such as pre-eclampsia, placental abruption and growth restriction were once thought to represent end-of-pregnancy issues. Currently, the cause of such complications are being increasingly recognised as defective implantation and placentation. The molecular mechanisms responsible for normal and abnormal implantation are an area of active investigation. Screening tests, such as Doppler ultrasound of the maternal uterine arteries and evaluation of markers in the maternal serum, are being assessed to determine if such tests might allow for better recognition and, perhaps, prevention of many pregnancy complications related to abnormal placentation. Many techniques during pregnancy have been used to prevent pregnancy complications such as pre-eclampsia. Most have been unsuccessful. Ultimately, the solution may reside in pre-pregnancy approaches to improve implantation and placentation. Such approaches are actively being investigated and have promise.

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Introduction

Human reproduction entails a fundamental paradox: although critical to the survival of the species, many aspects are inefficient and wastage seems excessive. Fecundity (the probability of pregnancy occurring within one menstrual cycle) peaks at around 30%,^{1,2} and only 50–60% of all conceptions advance beyond 20 weeks of gestation.³ Of those pregnancies lost, 75% fail to implant and are not recognised clinically.³ Normal implantation and placentation is thus critical for a successful pregnancy.

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It is self-evident that suboptimal implantation and placentation can lead to miscarriage. What is underappreciated, however, is that many pregnancy-related complications that present late in gestation (such as pre-eclampsia and preterm labour) seem to have their origins early in pregnancy, with abnormalities in implantation and placental development. Implantation is characterised by invasion of fetal trophoblast cells into the maternal tissues of the uterus, and the degree to which trophoblast invades the decidualised endometrium (decidua) and inner third of the myometrium seems to be a major determinant of pregnancy outcome. Inadequate invasion, specifically restricted endovascular invasion, has been implicated in the pathophysiology of such conditions as pre-eclampsia, preterm premature rupture of membranes (pPROM), preterm labour, and intrauterine growth restriction (IUGR).

Although the molecular mechanisms responsible for normal, abnormal implantation and placentation have not been fully delineated, screening tests have been developed in an attempt to identify pregnancies at high risk of developing complications. These tests include the use of Doppler ultrasound evaluation as well as maternal serum analyte analysis. It is hoped that a better understanding of the mechanisms involved in implantation and placentation will allow for the development of effective preventive strategies that may be used during the index pregnancy and during the inter-pregnancy interval. Such strategies may allow for the prevention of placenta-related complications, the attenuation of such insults and, ultimately, an improvement in pregnancy outcomes.

In this chapter, we include an overview of normal implantation followed by a discussion of a number of molecular mechanisms implicated in defective implantation and placentation. Current screening tests for defective implantation and placentation, such as uterine artery Doppler evaluation and maternal serum analyte assessment, will also be reviewed. Finally, putative preventive strategies will be discussed, including both intra- and inter-pregnancy approaches.

How abnormal placentation leads to adverse pregnancy outcomes

Normal implantation and placentation

Much of our understanding of early human development is inferred from animal studies. The initial stages of pre-implantation development, from fertilised ovum (zygote) to a solid mass of cells (morula), occur as the embryo transits the fallopian tube. Implantation occurs around days 6 to 7 after conception. Analogous to events in several primate species,^{4,5} human implantation most likely includes three stages. Initial adhesion of the blastocyst to the uterine wall (apposition) is unstable. During this stage, microvilli on the apical surface of syncytiotrophoblast interdigitate with microprotrusions (pinopodes) on the apical surface of the luminal epithelium. The next stage, stable adhesion, is characterised by increased physical interaction between the trophoblast and the uterine luminal epithelium. Shortly thereafter, invasion begins and syncytiotrophoblasts penetrate the uterine epithelium. By day 10 after conception, the blastocyst is completely embedded in subepithelial stromal tissue and the uterine epithelium grows to cover the implantation site.⁶ Shortly thereafter, mononuclear extravillous cytotrophoblasts stream out of the trophoblastic shell to invade the entire endometrium and inner third of the myometrium (interstitial invasion)⁷ as well as the maternal uterine vasculature (endovascular invasion).⁴ The latter process, which begins the process of placentation, establishes the definitive uteroplacental circulation and places fetal trophoblast in direct contact with maternal blood.

Regulation of trophoblast invasion

Complications that present relatively late in pregnancy (such as pre-eclampsia and preterm labour) seem to reflect errors that occur much earlier in placental development. Cytotrophoblast invasion to the proper depth is a major factor in determining pregnancy outcome. Excessive invasion resulting from a failure of the maternal tissues to restrain the invading cytotrophoblast cells² can lead to placenta accreta, increta or percreta. Inadequate invasion has been implicated in the pathophysiology of pre-eclampsia. Pre-eclampsia (gestational proteinuric hypertension) is the leading cause of maternal mortality in the industrialised world and increases perinatal mortality five-fold. Although the precise

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