

# Kofinas Perinatal

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## **The association between stillbirth in the first pregnancy and subsequent adverse perinatal outcomes (From the American Journal of Obstetrics and Gynecology 2009; 201; 378.e1-6)**

This study sought to examine the association between first pregnancy stillbirth and subsequent adverse perinatal outcomes. This study examined first two singleton deliveries at 20-44 weeks gestation from 1991-2008 (N=71,315) using birth certificate, hospitalization and outpatient encounter files. Multivariable logistic regression models (statistical models that examine the simultaneous interactions of multiple variables) were used to assess the association. The stillbirth was observed in 5.3 of 1000 first deliveries. There was an increased risk of an **ischemic placental disease, fetal distress, chorioamnionitis, extreme preterm birth, and early neonatal mortality in pregnancies after stillbirth versus pregnancies after live birth**. Interpregnancy intervals of less than 2 and more than 4 years after stillbirth increased the risk of an ischemic placental disease and a spontaneous preterm birth. Risks vary by stillbirth subtype. A first pregnancy stillbirth may increase adverse perinatal outcomes in subsequent pregnancies.

The findings of this study suggest that women whose first pregnancy resulted in stillbirth are at increased risk for ischemic placental disease, fetal distress, chorioamnionitis, spontaneous preterm birth and early neonatal mortality in the second pregnancy. Ante-partum stillbirth in the first pregnancy was associated with increased risk for ischemic placental disease in the second pregnancy. The interval between two pregnancies more defies the magnitude of associations with shorter and longer interpregnancy intervals resulting in an increased risk for adverse outcomes. The study further showed that women with a history of stillbirth were at higher risk of recurrence in subsequent pregnancy, an observation that is consistent with the findings of previous studies. Furthermore, consistent with the findings of this study of the association between prior stillbirth and subsequent preterm birth, Black et al recently reported a 2.5-fold increased risk for preterm birth in women with a prior preterm birth. However, unlike the findings of the present study Black's study did not show an association between stillbirth in the first pregnancy and a subsequent stillbirth and neonatal death.

Although the pathoetiologic mechanism by which ischemic placental disease, spontaneous preterm birth and stillbirth is not well understood, strong evidence suggests that genetic and environmental factors may contribute to etiologic mechanism of the disease. The current study showed that both shorter and longer interpregnancy intervals are associated with ischemic placental disease and spontaneous preterm birth in subsequent pregnancy. Although the mechanism underlying the association between first pregnancy stillbirth and a subsequent adverse pregnancy outcome remains speculative, findings of this study suggest that there may be a chronic inflammatory condition that may not have been resolved. In our judgment, this is a halfway conclusion. What causes the inflammation? The authors might imply that infection is the cause of the chronic inflammations as is the case in most reports. The problem with infection is that it is almost always the consequence of secondary contamination of the placenta during birth and not the primary cause of the inflammation. In our experience and based on our own research, placental inflammation is the result of placental necrosis caused by placental thrombotic degeneration. It is the existing thrombotic imbalances of the mother, the fetus and the father that are always there and affect future pregnancies. Of course, genetic thrombophilia does not affect all pregnancies. Every pregnancy is different even though the parents remain the same. Depending on whether genetic thrombophilia is of a homozygous or heterozygous state, every fetus will receive a different mixture of genes from each parent that might or might not affect his placenta. This is the reason why so many couples have successful pregnancies in the midst of

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multiple losses. Unless we understand that and monitor and treat every pregnancy with the same intensity we will never be able to prevent recurrent fetal loss (stillbirth or otherwise).

There are a number of other potential explanations of the findings. The maternal depletion hypothesis suggests that a short interpregnancy interval may not ensure sufficient time between subsequent pregnancies for the mother to recover from the nutritional burden and maternal stress. Hence, the uterine lining may not support a pregnancy conceived after a short pregnancy interval. This study has some limitations to consider. This explanation in today's abundant food environment and excellent prenatal care does not explain the relationship. Maternal depletion is a thing of the past and today it may only be encountered in severely deprived women in third world countries. Other deficiencies of this study include poor documentation of behavioral risk factors such as maternal obesity and smoking during pregnancy; smoking is known to cause placental thrombosis and necrosis.

One of the most flagrant omissions however is the profound lack of any information on placental condition, either prenatally or postnatally in regards to placental thrombosis. In our extensive experience with patients who suffered stillbirth, with the exception of cord accidents, all fetal deaths could be explained by thrombotic placental pathology. Such pathology is secondary to imbalances in maternal, fetal and paternal coagulations systems. Such imbalances cause variable degrees of placental thrombosis in both, maternal and fetal circulations. In conclusion, findings of this study suggest that a first pregnancy stillbirth may increase adverse pregnancy and early neonatal outcomes in subsequent pregnancy.

Clinical implications.

1. There is strong association between stillbirth in the first pregnancy and subsequent adverse outcomes.
2. The etiology of such adverse outcomes is usually chronic and recurrent. Maternal and / or paternal thrombotic conditions may be responsible.
3. The placenta should be thoroughly examined both, during pregnancy by means of ultrasound and after birth by means of pathologic examination. A pathologist experienced in perinatal pathology should be the only one involved in the assessment of the placenta.
4. Women with a history of stillbirth should be thoroughly investigated prior to pregnancy for thrombophilic abnormalities and if present, be treated accordingly during the pregnancy.
5. The best way to monitor future pregnancies in such patients is by means of fetal and maternal placental Doppler; this is the best and most reliable way to monitor treatment success and prevent perinatal adverse events.