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Placental pathology regarding inflammation and a new classification of stillbirth

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ABSTRACT

Background: The incidence of stillbirth has remained almost constant during the last 2-3 decades despite obvious improvements in obstetric care. To achieve a reduction of stillbirth, better understanding of the etiology is imperative. Relevant test protocols and audit work is reported to reduce the number of unexplained cases. Classification of death can help the audit group identifying relevant etiology and causes of fetal death. Since 1954 more than 35 classification systems for perinatal death have been published but there is still no international consensus. Few studies have investigated how causes of stillbirth differ over gestational ages, with varying and conflicting results. Infection is known as an important cause of stillbirth, particularly before gestational week (gw) 28. Various infections are thought to cause different forms of inflammation/infection in placenta. Bacterial infection is supposed to give a maternal inflammatory response in the placenta; histological chorioamnionitis (CAM) followed by a histological fetal response (FIR) including vasculitis (inflammation in vessels in the placenta and/or umbilical cord) and funisitis (inflammation in the Wharton's jelly), whereas a viral infection is supposed to cause chronic villitis. Histological CAM has shown to be clearly associated to stillbirth.

Method: In paper I "the Stockholm classification of stillbirth" is presented and validated regarding inter observer variability. In paper II, a cohort of all 1089 singleton pregnancies in Stockholm during a 12 year period was compared regarding primary and primary + associated cause of death, according to the classification. The cases were divided in early preterm (gw 22+0 to 28+6) and moderately preterm (gw 29+0 to 36+6) plus, term (gw 37+0 to 40+6) and post-term (gw ≥ 41+0). Two case-control studies including singleton placentas from 126 term stillborn cases and 273 live born controls (paper III) as well as 112 early preterm (gw 22+0 to 32+6) stillborn cases and 166 gestational week matched references (paper IV) were compared with focus on CAM, FIR and chronic villitis.

Results: We have developed a classification, exclusive for stillbirth, consisting of 17 groups of causes of death and allowing for one primary and several associated causes if needed. Most causes are graded in probability levels (definite, probable, or possible). The validated overall agreement regarding primary cause of death was substantial. When using the classification in the 12 year cohort of stillbirth, almost 90% of cases were ascribed a cause of death. Placental abruption and preeclampsia/hypertension were both more common as cause of death among preterm stillbirths compared to the term/post-term stillbirths, who showed a higher proportion of umbilical cord complications and infection. Infection was more common in post-terms compared to term stillbirths, and in extremely preterm compared to moderately premature stillbirths. In paper III we found CAM (especially severe), chronic villitis, villous immaturity, fetus who was small for gestational age (SGA) and maternal overweight, but not vasculitis or funisitis, to be independently associated with an elevated risk for stillbirth at term. In paper IV we found SGA and "CAM without FIR", but not "CAM with FIR," to be independently associated with a higher risk for stillbirth at early preterm gestation.

Conclusion: The Stockholm classification of stillbirth, primarily meant to be used by audit groups, has showed a low percentage of unclassifiable cases and a low inter observer variability. Knowledge about how causes of stillbirth are distributed over gestational ages could be clinically important and useful in developing strategies for prevention. Results in the case-control studies indicate that the presence of CAM, especially severe, is a risk factor for fetal death in term pregnancies whereas FIR is not. In early preterm pregnancies the presence of CAM is not a risk factor for fetal death if FIR exists, but it is a threat to the fetus if FIR does not occur. Further research is needed to clarify if the development of FIR is actually protecting the fetus from death, a finding that of course could be of great importance for the understanding of the mechanisms of stillbirth.

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