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Stillbirth, hypertensive disorders of pregnancy, and placental pathology

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ABSTRACT

Introduction: Stillbirth, preeclampsia, and gestational hypertension (PE/GH) have similar clinical risk factors and redundant placental pathology. We aim to discern if stillbirth with PE/GH has a particular phenotype by comparing stillbirths with and without PE/GH.
Methods: Secondary analysis of the Stillbirth Collaborative Research Network, a population-based cohort study of all stillbirths and a sample of live births from 2006 to 2008 in five catchment areas. We compared placental pathology between stillbirths and with and without PE/GH, stratified by term or preterm. We also compared placental pathology between stillbirths and live births with PE/GH.
Results: 79/518 stillbirths and 140/1200 live births had PE/GH. Amongst preterm stillbirths, there was higher feto-placental ratio in PE/GH pregnancies (OR 1.24 [1.11, 1.37] per unit increase), and there were more parenchymal infarctions (OR 5.77 [3.18, 10.47]). Among PE/GH pregnancies, stillbirths had increased maternal and fetal vascular lesions, including retroplacental hematoma, parenchymal infarction, fibrin deposition, fetal vascular thrombi, and avascular villi.
Discussion: Stillbirth pregnancies are overwhelmingly associated with placental lesions. Parenchymal infarctions are more common in PE/GH preterm stillbirths, but there is significant overlap in lesions found in stillbirths and PE/GH.

1. Introduction

Stillbirth is a major concern, affecting 6 per 1000 pregnancies in the United States [1] Preeclampsia is a common obstetric disorder, occurring in 2%–7% of pregnancies [2,3] and is a major risk factor for stillbirth, increasing the odds by 1.2–4.0 fold [4–7]. The rate of stillbirth in women with preeclampsia in high-income countries is estimated as 0.3–1.9%, although it was previously as high as 4.4–7% [8–10]. Hypertensive disorders contribute to 9.2% of stillbirths in a contemporary cohort [1]. Risk factors for the two overlap, including obesity, pre-gestational diabetes mellitus, lupus, renal disease, advanced maternal age, nulliparity, non-Hispanic black race, and multifetal gestation [2,12–14].

Placental insufficiency is often implicated in stillbirth, particularly in the setting of preeclampsia. Placental insufficiency is when

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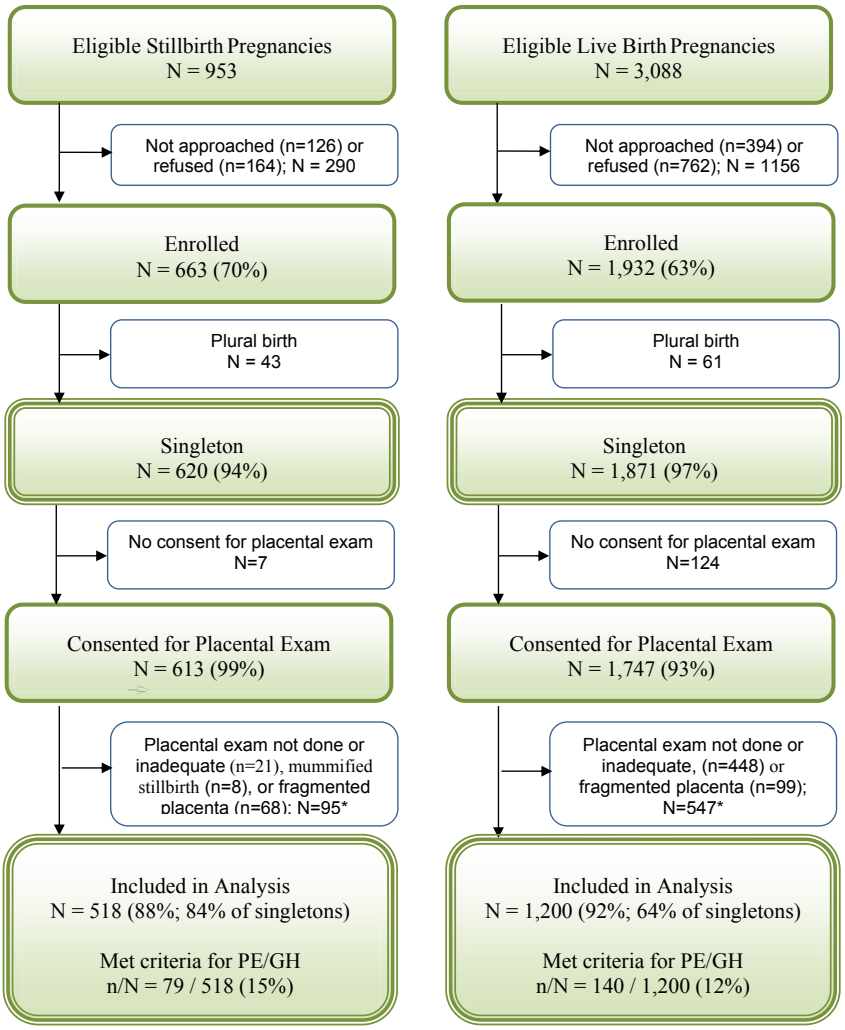

Fig. 1. This analysis compares placental examination results for subgroups of singleton stillbirth and live birth pregnancies, with particular focus on PE/GH. A pregnancy was categorized as a stillbirth pregnancy if there were any stillbirths delivered and as a live birth pregnancy if all live births were delivered. A fetal death was defined by Apgar scores of 0 at 1 and 5 min and no signs of life by direct observation. Fetal deaths were classified as stillbirths if the best clinical estimate of gestational age at death was 20 or more weeks. Fetal deaths at 18 and 19 weeks without good dating were also included as stillbirths. * A placenta examination was deemed inadequate for this analysis if conducted by a pathologist other than those trained to follow the Stillbirth Collaborative Research Network placental exam protocol or if only slides were available for review. Mummified stillborn fetuses were those with Grade IV–V maceration among fragmented fetuses and Grade V maceration among intact fetuses. Two stillborn fetuses were both fragmented and macerated.

a maladaptive placenta fails to provide adequate oxygen and nutrients to the growing fetus, leading to both adverse obstetric sequelae and fetal programming [15]. The pathophysiology of placental insufficiency includes abnormal trophoblast invasion or placental damage, leading to decreased placental perfusion [16–20]. Placental lesions can be divided into “maternal malperfusion” or “fetal vascular abnormalities”. Maternal malperfusion lesions involve the maternal circulation, such as abnormal maternal vasculature, parenchymal infarct or thrombus, and intervillous/perivillous lesions. Fetal vascular abnormalities reflect lesions on the fetal side of the placenta, including abnormal development or thrombus/infarct of the fetal vasculature within the placenta [21].

In case-control studies, lesions consistent with both maternal vascular malperfusion and fetal vascular abnormalities have been noted more frequently in placentas from women with early onset, severe preeclampsia. These include decidual vasculopathy, infarcts, distal villous hypoplasia, and excessive syncytial knots [19,22–24]. Placentas in preeclamptic pregnancies are also typically smaller for gestational age than those from normal pregnancies (20). Early-onset preeclampsia appears to have a more severe placental phenotype than late-onset preeclampsia [25,26].

Because of this, we believe placental pathology in stillbirths associated with preeclampsia will be different than stillbirths not associated with preeclampsia. We aim to compare placental pathology 1) in stillbirths with and without preeclampsia and 2) in stillbirths with preeclampsia and live births with preeclampsia (and we speculate that this latter comparison will be similar).

2. Methods

This is a subanalysis of a population-based case-control study of stillbirth conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Stillbirth Collaborative Research Network [27]. Participants were enrolled at delivery between March 2006 and September 2008. There were five catchment areas defined by state and county boundaries, including Rhode Island and portions of Massachusetts, Georgia, Texas, and Utah. 59 hospitals participated, ensuring access to at least 90% of