Best Practice & Research Clinical Obstetrics and Gynaecology xxx (2018) 1–14

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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Examining the link between placental pathology, growth restriction, and stillbirth

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Keywords:
Growth
Restriction
Stillbirth
Placenta

A B S T R A C T

Stillbirth, often defined as death of a fetus ≥20 weeks of gestation, is emotionally devastating for families and caregivers. It is often associated with fetal growth restriction (FGR). Indeed, FGR or small-for-gestational age fetus (SGA) is a major risk factor for stillbirth. In rare cases, this is due to genetic abnormalities or infections. However, in most cases, it is linked to placental insufficiency. This may be due to abnormal placental development or placental damage, thereby resulting in decreased blood flow, oxygen, and nutrients to the fetus. Several placental histological abnormalities are associated with stillbirth, FGR, or both. Most involve vascular abnormalities but some are inflammatory lesions. This paper reviews evidence regarding the relationships between placental function and pathology, FGR, and stillbirth. Issues with clinical relevance, knowledge gaps, and areas for further research are highlighted.

Stillbirth is a tragedy for families and clinicians. There are an estimated 3.2 million stillbirths at 28 weeks or more of gestation occurring worldwide annually [1]. Further, approximately 98% of all stillbirths occur in low- and middle-income countries [1].The stillbirth rate in the U.S. in 2013 was 5.96 per 1000 births [2]. The rate declined from 6.61 to 6.05 per 1000 births from 2000 through 2006 and has remained relatively stable in the past decade [3].The rate is even lower in other high-resource settings. For example, in 2016, the stillbirth rate in the U.K. was 4.4 per 1000 births [4]. (see Table 3)

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https://doi.org/10.1016/j.bpobgyn.2018.03.004
1521-6934/

Please cite this article in press as: Silver RM, Examining the link between placental pathology, growth restriction, and stillbirth, Best Practice & Research Clinical Obstetrics and Gynaecology (2018), https://doi.org/10.1016/j.bpobgyn.2018.03.004

One of the most important risk factors for stillbirth, especially in high-resource settings is fetal growth restriction (FGR). Numerous case–control studies demonstrate a several fold increase in the risk for stillbirth in small-for-gestational age (SGA) fetuses [5–8].A similar association has been confirmed in prospective studies [9–11].A recent meta-analysis noted a population attributable risk percent of 23% for FGR and stillbirth [12].

Q3 There are many potential pathways for the association between stillbirth, FGR, and SGA. In most cases, FGR is thought to be a marker for uteroplacental insufficiency. Decreased placental function (either due to abnormal development, damage, or both) leads to decreased blood flow, oxygen, and nutrients to the fetus. In turn, this results in decreased fetal growth. Maternal medical conditions associated with decreased placental function such as hypertension, diabetes, renal disease, and systemic lupus erythematosus are associated with FGR. Smoking also is linked to FGR through decreased placental blood flow. FGR is also associated with other conditions linked to stillbirth including fetal genetic abnormalities, birth defects, multifetal pregnancy, and infections such as cytomegalovirus infection. Accordingly, there is considerable biological plausibility for the relationship between FGR and stillbirth.

It is important to recognize that FGR or SGA is a risk factor for, rather than a "cause" of stillbirth. Indeed, the vast majority of SGA and FGR fetuses are live born. Moreover, it is difficult to define SGA and FGR, and most definitions include entirely normal fetuses that are smaller than normal. These fetuses are referred to as being "constitutionally small."

SGA is easier to define than FGR. Typically, it is defined as estimated fetal weight (EFW) based on obstetric sonogram or the birth weight (e.g., below the 10th or the 5th percentile of the population, or <2 standard deviations below mean [around the 3rd percentile]). By design, this definition captures a large number of entirely normal fetuses that happen to be in the lowest percentile for fetal weight. Importantly, accurate determination of SGA fetuses requires precise knowledge of gestational age. In cases with assisted reproductive technology, good prenatal care, and/or obstetric sonogram performed early in gestation, it is easy to determine reliable gestational age. However, this is not always the case. Determination of gestational age may be difficult and inaccurate in pregnancies with little or no prenatal care.

Another problem with the assessment of SGA is an interval between death of the fetus and delivery of the fetus. Some studies of SGA assumed that delivery occurs within days of fetal death [5]. However, this may overestimate gestational age at death, thus increasing the proportion of SGA stillbirths. A recent study noted that careful assignment of gestational age at death using an algorithm involving gestational age, clinical timing of death, autopsy, and foot length was during one or more weeks before delivery in 43.5% of stillbirths [13]. There was good correlation between gestational age estimated from foot length and that estimated from the algorithm (within 2 weeks for 75% of cases) [13]. This algorithm and foot length [14] can be used to more precisely ascertain the gestational age at death, in turn allowing for more accurate determination of SGA.

A recent investigation attempted to quantify the effects of intrauterine retention and postmortem interval on SGA fetus in stillbirth [15]. In a cohort of 533 stillbirths after 24 weeks of gestation, there was a strong relationship between increasing time from death to delivery and reduction in birthweight. The average artifactual reduction in birthweight was estimated as −0.8 SD of the expected weight. In addition, there was a 12% reduction on average in fetal weight between delivery and autopsy, showing increasing reduction with increasing delivery-to-autopsy duration [15]. Thus, the interval between delivery and
Q4 autopsy should be considered along with death-to-delivery interval when evaluating fetal weight.

FGR is difficult to define, and there is no universally accepted definition. It can be defined as the failure of the fetus to reach its growth potential. However, as we do not currently have a good method to establish growth potential, how can we define failure to attain it? Because of this, definitions of FGR used in clinical practice differ widely [16–18].Thus, although FGR is often defined using EFW percentiles, a fetus with an EFW >10% for gestational age may be FGR based on growth percentile [19].

The overarching goal is to identify fetuses at risk for adverse pregnancy outcomes including stillbirth. Accordingly, numerous additional biophysical, clinical, and biomarker parameters also have been used to define FGR. These include serial measurements of biometry to assess declining growth; assessment of flow to the uterus, through the umbilical cord and in the fetus; and serum proteins
Q5 [16–18,20–22]. These are discussed at length in other chapters in this symposium.

Please cite this article in press as: Silver RM, Examining the link between placental pathology, growth restriction, and stillbirth, Best Practice & Research Clinical Obstetrics and Gynaecology (2018), https://doi.org/10.1016/j.bpobgyn.2018.03.004