Received: 13 December 2018 | Revised: 28 October 2019 | Accepted: 29 October 2019

DOI: 10.1002/ajmg.a.61426

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

Fetoplacental ratios in stillbirths and second trimester miscarriages

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Abstract

An abnormal fetoplacental (F/P) ratio is a risk factor for poor pregnancy outcomes including fetal death, but studies of F/P ratio among stillbirths are limited. In the Wisconsin Stillbirth Service Program cohort of second and third trimester fetal deaths, 1,022 were at ≥24 weeks with data on fetal and placental weight. Comparison with data for viable infants of the same gestational ages (GAs) showed that the F/P ratio increases more rapidly with GA for stillbirths than for viable infants. While placentas of stillborn infants are small at all GA, weights of deceased fetuses are lowest early in the second trimester, becoming nearly normal by term. Excess high F/P ratios are noted at all GAs, increasing toward term, while low ratios are frequent at early gestation but rare near term. Analysis by cause of death shows that F/P ratios are markedly elevated for placental and maternal causes (about 50% above the 90th centile), somewhat elevated for cord accidents, non-hydropic fetal, and unknown causes (about 1/3 above the 90th centile), and variable with 40% below the 10th centile for hydropic stillbirths. Across all causes and GAs, placental weights are more abnormal than fetal weights, suggesting that diminished placental function may contribute to fetal demise even when non-placental causes (e.g., premature membrane rupture, cord accidents, and chromosomal disorders) are identified. About half of all stillbirths have abnormal F/P ratios, suggesting that improvements in prenatal assessment of placental size and function might aid in identifying pregnancies at risk for demise; unfortunately, therapeutic options for ongoing pregnancies with diminished placental function remain limited.

KEYWORDS

fetal death, fetoplacental ratio, miscarriage, stillbirth

1 | INTRODUCTION

Small for gestational age (GA)/fetal growth restriction (FGR) is a major risk factor for stillbirth (Bukowski et al., 2014; Silver, 2018). Large for GA fetuses, however, are also at increased risk (Bukowski et al., 2014). Due to the correlation between fetal and placental weights, fetoplacental (F/P) ratio is frequently used to identify pregnancies with disproportionately large or small placentas relative to fetal weight. The association of abnormal F/P ratios with perinatal morbidity and mortality has been recognized for many years (Bonds, Gabbe, Kumar, & Taylor, 1984; Naeye, 1987), but only a few studies have specifically addressed placental size and F/P ratio in stillbirth. Haavaldsen, Samuelsen, and Eskild (2013), using data from the Norwegian birth registry, reported that pregnancies with placentofetal (P/F) ratios in the highest and lowest quartiles were overrepresented among 1,058 preterm fetal deaths compared with 28,759 live births at comparable GAs, while only P/F ratios in the lowest quartile were overrepresented among 797 term stillbirths compared with 504,278

term live births in the same population. In a smaller population of only 145 stillbirths, Pásztor, Sikovanyecz, Keresztúri, Kozinszky, and Németh (2018) found no relationship between F/P ratio and cause of death. Because the F/P ratio alone may miss circumstances where fetal and placental weights are both very large or very small, studies of fetal and placental weights as well as F/P ratio provide more understanding of the contribution of fetal and placental growth to perinatal morbidity and mortality. Hutcheon, McNamara, Platt, Benjamin, and Kramer (2012) noted that after correction for fetal weight, small placental size remains an independent risk factor for adverse perinatal outcomes including stillbirth. In the current study, fetal and placental weights and F/P ratios in a population of 1,684 stillborn infants and fetuses were analyzed by GA and cause of death.

2 | METHODS

The Wisconsin Stillbirth Service Program (WiSSP) database contains records of 3,137 stillbirths and second trimester miscarriages referred for etiologic evaluation between 1983 and 2017. Data include maternal records, clinical fetal examinations, photographs, babygram anteroposterior and lateral radiographs, chromosomal or other laboratory results, autopsy, and placental pathology reports. This information was sent to a central location for evaluation by a board-certified clinical geneticist with a specific interest in stillbirth. Causes of death, which were classified as fetal, placental, and/or maternal, were reported back to the referring provider. With the approval of the Institutional Review Board, data were stored in a searchable database for future research.

After exclusion of multifetal pregnancies and cases with missing data on fetal or placental weights, 1,683 cases were manually reviewed. For the 1,022 stillbirths at 24 weeks or greater, comparisons were made with data for over 500,000 singleton live births in Norway (Thompson, Irgens, Skjaerven, & Rasmussen, 2007), which include percentile curves for fetal weight, placental weight, and F/P ratio for male and female infants at GAs from 24 to 44 weeks. To maintain adequate size in all subgroups, stillborn fetuses were not separated by gender. Therefore, male and female data from the comparison group were averaged. Because the male/female ratio in the stillborn group is 1.00, compared with 1.05 in the control data, any bias due to averaging of male and female data is likely to be minimal. For GAs prior to viability, no comparable control data with percentile curves for F/P ratios have been published. The most reliable birthweight data for infants dying neonatally at 20–23 weeks (Jones, Harrison, & Smith, 2004) unfortunately contains no information on placental weights. The best placental data available for previable fetuses are on the curve published by Hall and colleagues (Hall, Froster-Iskenius, & Allanson, 1989), which is not only based on a different population but presumably combines stillbirths and neonatal death. Due to the uncertainties inherent in this calculation, the approximated "neonatal death" F/P ratios at 20–23 weeks were used only for comparison with stillborn mean F/P ratios at the same GAs. Stillbirths before 24 weeks were excluded from the analysis of F/P ratio distributions by GA or cause of death. For miscarriages before 20 weeks, F/P ratios were not calculated due to the lack of any normal standards or live birth data for comparison.

For analysis by cause of death, subgroups within the WiSSP cohort were compared and contrasted. Following manual review of each case, mechanisms of demise were classified as fetal without hydrops, fetal with hydrops (called "hydrops" regardless of chromosomal or other anomalies), placental (mostly abruption, large infarcts, placental insufficiency), umbilical cord, maternal (mostly premature rupture of membranes and chorioamnionitis), and unknown. Fetuses with two causes identified were included in both groups. To facilitate comparison between etiologic groups that spanned a range of GAs, the fetal weight, placental weight, and F/P ratio of each stillborn infant was classified as below the 10th centile, at the 10th to 90th centile, or above the 90th centile reported for live-born infants of the same GA.

3 | RESULTS

In pregnancies with fetal demise, the mean F/P ratio increases more rapidly with GA than it does in viable pregnancies (Figure 1). From 36 weeks onward, the mean F/P ratio for stillbirths is above the 90th centile for live-born infants at the same GA.

In the late second and early third trimester, weights of stillborn fetuses are low compared with viable infants at the same GA (with about half below the 10th centile), but near-term stillborn infants are almost as large as their live-born counterparts (Table 1). The number of stillborn infants above the 90th centile is close to expected, always remaining below 20% (Table 1).

Placentas of stillborn infants are much smaller than those of viable infants at all GAs. The numbers of stillborn placental weights below 10th centile range from 46% at 24–27 weeks, 45% at 28–31 weeks, and 53% at 32–35 weeks, to 61% at 36 weeks or greater. Week by week comparisons are listed in Table 1. Large placentas are rare in stillbirths, remaining less than the expected 10%, except at 32 weeks when there is a small peak (Table 1).

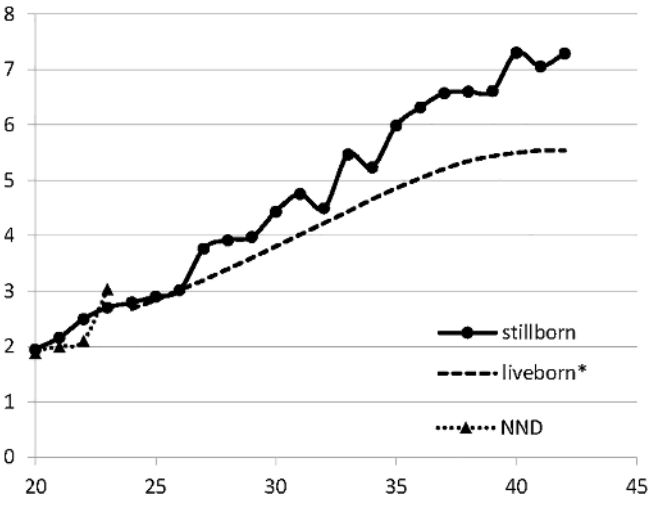

FIGURE 1 Mean fetal/placental ratio by gestation

TABLE 1 Fetal and placental weights and F/P ratio distribution for stillborn infants compared with live births at the same gestational age

GA	*n*	Fetus < 10th	Fetus 10th–90th	Fetus > 90th	Placenta < 10th	Placenta 10th–90th	Placenta > 90th	F/P < 10th	F/P 10th–90th	F/P > 90th
24	82	46 (56%)	24 (29%)	12 (15%)	41 (50%)	41 (50%)	0 (0%)	20 (24%)	44 (52%)	18 (22%)
25	47	32 (68%)	14 (30%)	1 (2%)	20 (43%)	25 (53%)	2 (4%)	10 (21%)	27 (57%)	10 (21%)
26	44	28 (64%)	14(32%)	2 (5%)	22 (50%)	19 (43%)	3 (7%)	15 (34%)	17 (39%)	12 (27%)
27	46	23 (50%)	23 (50%)	0 (0%)	18 (39%)	27 (59%)	1 (2%)	9 (20%)	22 (48%)	15 (33%)
28	52	23 (44%)	26 (50%)	3 (6%)	24 (46%)	24 (46%)	4 (8%)	8 (15%)	31 (60%)	13 (25%)
29	39	12 (31%)	23 (59%)	4 (10%)	17 (44%)	19 (49%)	3 (8%)	11 (28%)	18 (46%)	10 (26%)
30	37	15 (41%)	17 (46%)	5 (14%)	18 (49%)	16 (43%)	3 (8%)	6 (16%)	21 57%)	10 (27%)
31	44	9 (20%)	28 (64%)	7(16%)	19 (43%)	22 (50%)	3 (7%)	10 (23%)	14 (32%)	20 (45%)
32	47	11 (23%)	27 (57%)	9 (19%)	21 (45%)	16 (34%)	10 (21%)	17 (36%)	16 (34%)	14 (30%)
33	54	13 (24%)	35 (65%)	6 (11%)	29 (54%)	25 (46%)	0 (0%)	3 (6%)	33 (61%)	18 (33%)
34	57	17 (30%)	36 (63%)	4 (7%)	33 (58%)	22 (39%)	2 (4%)	14 (25%)	25 (44%)	18 (32%)
35	46	9 (20%)	33 (72%)	4 (9%)	26 (57%)	19 (41%)	1 (2%)	4 (9%)	24 (52%)	18 (39%)
36	67	16 (24%)	44 (66%)	7 (10%)	44 (66%)	19 (28%)	4 (6%)	6 (9%)	34 (51%)	27 (40%)
37	81	15 (19%)	55 (68%)	11(14%)	51 (63%)	28 (35%)	2 (2%)	7 (9%)	34 (42%)	40 (49%)
38	88	13 (15%)	66 (75%)	9 (10%)	45 (51%)	42 (52%)	1 (1%)	4 (5%)	44 (50%)	40 (45%)
39	66	14 (21%)	45 (68%)	7 (11%)	38 (58%)	24 (36%)	4 (6%)	8 (12%)	27 (41%)	31 (47%)
40	73	11 (15%)	58 (79%)	4 (5%)	48 (66%)	24 (33%)	1 (1%)	3 (4%)	30 (41%)	40 (55%)
41	37	1 (3%)	35 (95%)	1 (3%)	23 (62%)	13 (35%)	1 (3%)	3 (8%)	15 (41%)	19 (51%)
42	15	2 (13%)	12 (80%)	1 (7%)	12 (80%)	3 (20%)	0 (0%)	3 (20%)	5 (33%)	7 (47%)

Abbreviations: F/P, fetoplacental; GA, gestational age (weeks).

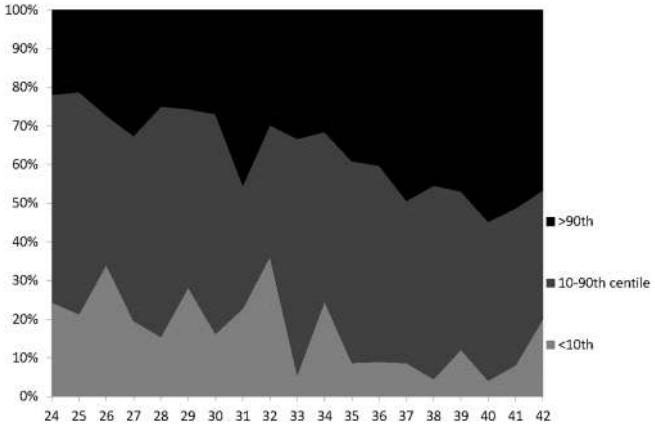

FIGURE 2 Stillborn fetal/placental (F/P) ratio relative to live-born norms. F/P ratios above the 90th centile are more frequent than expected for all ages, increasing from about 20% at early gestation to about 50% at term. F/P ratios below the 10th centile are increased to just over 20% in early gestation, decreasing to less than the expected 10% by term. Fewer than half of all stillborn fetuses have F/P ratios between the 10th and 90th centile

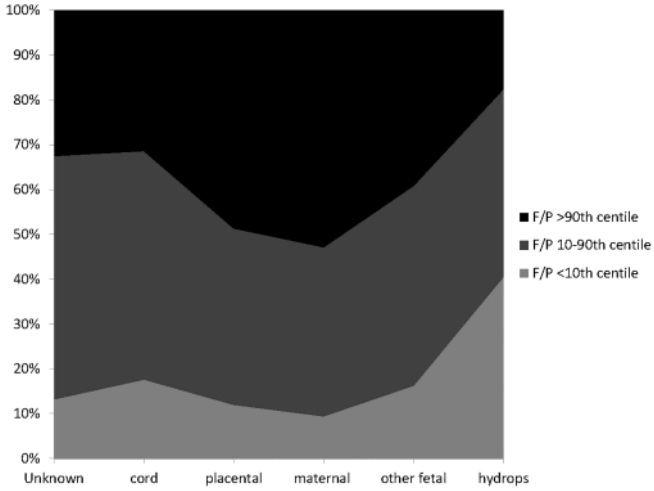

FIGURE 3 Fetal/placental (F/P) ratio by cause of death. F/P ratios above the 90th centile are more frequent than expected for all causes of fetal death, especially in the placental and maternal where almost half of all stillbirths have elevated F/P ratios. Low F/P ratios are increased for hydropic fetuses only, but normal for all other causes of death

Early in the third trimester when the mean appears normal, the distribution of F/P ratios for pregnancies resulting in stillbirth is unusual, with about one-fourth below the 10th centile, one-fourth above the 90th centile, and only half between the 10th and 90th centile for live-born infants (Table 1). With increasing GA, the number of low F/P ratios decreases, while the number of high ratios increases to about 50% by term (Figure 2). Overall, only 47% of stillborn infants in the WiSSP cohort have F/P ratios between the 10th and 90th centile for GA (Table 1).

When stillbirths were grouped by apparent cause, all causal categories had more than expected fetuses with F/P ratios above the

TABLE 2 Fetoplacental (F/P) ratios, fetal and placental weights of stillborn infants by cause of death: Comparison with live-born centiles

	Unknown	Cord	Placental	Maternal	Other fetal	Hydrops	Totals
F/P < 10th	59 (13%)	9 (18%)	32 (12%)	5 (9%)	27 (16%)	30 (41%)	162
F/P 10–90th	242 (4%)	26 (51%)	105 (39%)	20 (38%)	74 (45%)	31 (42%)	498
F/P > 90th	145 ((33%)	16 (31%)	130 (49%)	28 (53%)	65 (39%)	13 (18%)	397
F < 10th	109 (24%)	10 (20%)	110 (41%)	7 (13%)	68 (41%)	15 (20%)	319
F 10–90th	310 (70%)	40 (78%)	136 (51%)	38 (72%)	71 (43%)	38 (51%)	633
F > 90th	27 (6%)	1 (2%)	21 (8%)	8 (15%)	27 (16%)	21 (28%)	105
P < 10th	224 (50%)	21 (41%)	183 (69%)	23 (43%)	97 (58%)	19 (26%)	567
P 10–90th	211 (47%)	28 (55%)	78 (29%)	30 (57%)	65 (39%)	31 (42%)	443
P > 90th	11 (2%)	2 (4%)	6 (2%)	0 (0%)	4 (2%)	24 (32%)	319
Totals	446	51	267	53	166	74	1,057

90th centile for liveborns at comparable GAs (Figure 3). The excess of high F/P ratios was most evident for maternal and placental causes, where about half of observed F/P ratios were above the 90th centile for live births, intermediate for unknown, cord, and other fetal causes where about one-third were above the 90th centile, and least for hydropic stillbirths where about only 18% exceeded the 90th centile (Table 2). Low F/P ratios below the 10th centile were observed in 41% of hydropic stillbirths, but were less than 20% for all other etiologic groups.

In all etiologic groups, the number of small fetuses was greater than expected. This difference was most striking in the placental and non-hydropic fetal groups, in each of which 41% of stillborn fetuses had weights below the 10th centile for live births at the same GA, intermediate in the placental, cord, hydropic, and unknown groups (all with 20–25% below the 10th centile, and trivial in the maternal group where only 13% were below the 10th centile (Table 2). The number of large fetuses was close to expectations (2–16% above the 90th centile) for all groups, except the hydropic stillbirths where 28% exceeded the 90th centile.

In all causal categories of stillbirth, the distribution of placental weights was more abnormal than that for stillborn fetuses (Table 2). Most strikingly, in the placental cause group, 69% of placental weights were below the 10th centile, while only 2% exceeded the 90th centile. In the non-hydropic fetal group, 58% of placentas were small, and only 2% were large. In the maternal cause group where fetal weights were nearly normal, 43% of placental weights fell below the 10th centile, while none were above the 90th. In the group with umbilical cord "accidents," 43% of placentas were below the 10th centile, and only 4% were above the 90th. The hydropic stillbirths showed a different placental weight distribution with excesses of both large and small placentas.

4 | DISCUSSION

Overall, there is an excess of high F/P ratios among stillborn infants at all GAs and across all causes of fetal death. This strongly suggests that relative placental insufficiency or diminished placental reserves may contribute to stillbirth, even when other causes such fetal. malformations, premature rupture of membranes with chorioamnionitis, or cord accidents are identified. High F/P ratios in the WiSSP cohort appear to be due to small placentas, which are much more frequent than expected at all GAs. The number of large fetuses is only slightly, if at all, increased compared with data for viable infants and is always much less than the number of high F/P ratios at the same GA. The observed excess of high F/P ratios, especially at term, strongly suggests that deficient placental growth frequently precedes fetal death and may be a warning sign of impending stillbirth.

The WiSSP data also confirm the excess low F/P ratios in preterm fetal death, but not in full term fetal deaths which was initially reported by Haavaldsen et al. (2013).

The increased number of low F/P ratios in preterm stillbirths mirrors the distribution of fetal weights in the WiSSP cohort, which tend to be low at early GAs but normalize by term. Increased placental weight is rare in the stillborn cohort (except for a small peak at 32 weeks) and, therefore, cannot contribute to the observed excess of low F/P ratios at early GAs. While decreased F/P ratio could be artefactual if recognition of fetal death is delayed while the placenta continues to grow, this seems improbable, because the findings in WiSSP are similar to the Norwegian study (Haavaldsen et al., 2013) where pregnancies were closely monitored by ultrasound, making prolonged intrauterine retention of a deceased fetus very unlikely. Low birthweight relative to placental weight in a stillborn fetus suggests that the fetus, but not the placenta, may have ceased growth prior to demise. The distribution of F/P ratios in the WiSSP cohort suggests that abnormalities with disproportionate effects on fetal growth are common in preterm fetal demise, but not in stillbirths near term.

The observation that only about half of all stillborn infants have an F/P ratio in the "normal" range (10th to 90th centile for viable births) suggests that the balance between fetal and placental growth is a major contributor to fetal survival. In preterm stillbirths, when both fetuses and placentas tend to be small relative to viable pregnancies at the same GA, the excess of low F/P ratios suggests a mechanism that disproportionately affects fetal growth, even though the placenta may also be small, while the excess of high F/P ratios suggests a different mechanism that affects the placenta more severely than the fetus. Near term, stillborn fetuses have weights similar to

viable infants of the same GA; the excess of high F/P ratios implies limitation of placental growth prior to demise of the fetus.

Since, at least for preterm infants, the distribution of F/P ratios in the WiSSP sample suggests multiple mechanisms contributing to fetal death, it seems possible that F/P ratio might help to identify broad categories of causes. Low F/P ratios might suggest "fetal" causes, while high ratios might direct investigation toward "placental" causes. Essentially normal F/P ratios might be expected for maternal and umbilical cord causes. While Pásztor et al. (2018) did not note any significant differences in mean placentofetal ratios between different categories of causes in a sample of 145 singleton stillbirths, they did not consider the distribution of ratios. Furthermore, their study may have been underpowered to detect such differences. The WiSSP cohort, with over 1,000 stillbirths at or after 24 weeks already categorized into broad causal groups, provided an ideal sample to retest the hypothesis that F/P ratio might differ according to the cause of fetal death.

As expected, the group with identified placental causes had an excess of high F/P ratios; however, the group with maternal causes had a very similar distribution of F/P ratios. When placental causes are identified, the fetuses are small, but the placentas are even smaller, resulting in almost half the group having F/P ratios above the 90th centile for live births. In contrast, when the cause is maternal, the fetuses are essentially normal in size, but the placentas are small and again about half the group has F/P ratios above the 90th centile. These findings strongly suggest that even though immediate cause of fetal death appears to be maternal, an underlying abnormality has already affected placental growth. Effectiveness of treatments directed at preventing maternal causes of stillbirth such as premature rupture of membranes and chorioamnionitis may be diminished due to underlying placental abnormalities.

Not as dramatic, but still notable, was the excess of high F/P ratios among fetuses that had died due to umbilical cord "accidents." If these were really sudden random events, the F/P ratios should be normal, but almost one-third had F/P ratios above the 90th centile for live-born infants, raising the possibility that diminished placental reserves may contribute to demise from umbilical cord obstruction. This could occur if fetuses with mild hypoxia are less able to tolerate partial cord obstruction. Alternatively, since excessive fetal movement has been reported as a sign of acute fetal compromise (Heazell, Stacey, O'Brien, Mitchell, & Warland, 2018), the possibility that less severe fetal stress results in increased fetal activity contributing to cord entanglement could also be considered.

Non-hydropic infants dying from fetal causes, as expected, tend to be small, but contrary to our starting hypothesis, F/P ratios are not reduced; in fact, their placentas are also small, resulting in an excess of high F/P ratios. The small placentas in this group presumably reflect the effects of chromosomal or other genetic conditions on placental growth. The high rate of demise for fetuses with severe chromosomal or Mendelian disorders even when no specific life-limiting malformations are identified may reflect effects of underlying genetic disorders on placental growth and function. In contrast, hydrops (regardless of underlying cause) is the only group with a marked excess of low F/P ratios, due presumably to increased weight of some hydropic fetuses. There is, however, a U-shaped distribution of fetal weight, placental weight, and F/P ratio with both more high and more low values than expected in the hydropic group. The major effects of hydrops on the distribution of fetal weights and F/P ratios justify the decision to treat hydrops as a discrete group, even when underlying chromosomal or other fetal anomalies were identifiable.

Fetal/placental ratio is an area deserving of further study, particularly in pregnancies resulting in fetal death. The major strength of the current study is the large number of stillbirths with data on GA, fetal and placental weights, and etiologic evaluation for 1,623 stillbirths, of which 1,022 occurred after 23 weeks. This is the only study of sufficient size to demonstrate differences in F/P ratio by cause of death. Limitations include the scarcity of control data for live births. No birthweight data with linked placental weights are available for Wisconsin, and thus, data from Norway were used. Prior to viability, it is difficult to define any control group, since placental weights cannot be reliably measured in ongoing pregnancies. Furthermore, being retrospective, the observation of abnormal F/P ratios following delivery of a deceased fetus can only be applied to the long term goal of prediction and prevention of stillbirth if F/P ratios can be estimated in ongoing pregnancies.

Ultrasound estimation of placental size could potentially serve as a screening tool to identify pregnancies at risk for stillbirth. The utility of such an approach, however, would depend on the accuracy of ultrasound for placental evaluation as well as the availability of safe and effective intervention for pregnancies at risk. Unfortunately, current ultrasound estimations of placental weight are not sufficiently accurate for clinical use (Higgins, Simcox, Sibley, Heazell, & Johnstone, 2016). Furthermore, the WiSSP data address placental weight after demise has occurred. Prospective studies are necessary to determine whether there is an optimal time window in which detection of placental changes can identify pregnancies at risk for stillbirth to direct additional testing or intervention.

Other than the possibility of early delivery, which would have to be balanced against risks of prematurity, there are no generally accepted treatments for placental insufficiency in an ongoing pregnancy. Even early delivery is controversial, since meta-analysis shows insufficient evidence that early delivery of term infants with other types of compromise (such as FGR or decreased fetal movement) changes mortality and morbidity (Bond et al., 2015). Because placental imaging is not part of routine prenatal care, pregnancies with small placentas are only occasionally recognized prior to delivery, usually as part of evaluation for fetal growth retardation. To investigate potential interventions, pregnancies with normal fetal weights but high F/P ratio would need to be identified prospectively.

The WiSSP data do not lead to any immediate clinical recommendations to reduce the incidence of stillbirth; it does suggest that the placenta is a major contributor to stillbirth, even when non-placental causes are identified. Further research is needed to fully understand the role of the placenta in causing and contributing to stillbirth.

CONFLICT OF INTEREST

None to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: McPherson E. Fetoplacental ratios in stillbirths and second trimester miscarriages. *Am J Med Genet Part A*. 2020;182A:322–327. https://doi.org/10.1002/ajmg.a.61426