RESEARCH ARTICLE

Stillbirths at Term: Case Control Study of Risk Factors, Growth Status and Placental Histology

Federico Mecacci¹, Caterina Serena¹*, Laura Avagliano², Mauro Cozzolino³, Eleonora Baroni¹, Marianna Pina Rambaldi⁴, Serena Simeone¹, Francesca Castiglione⁴, Gian Luigi Taddei⁴, Gaetano Bulfamante²

¹ Department of Sciences for the Health of Women and Children, Careggi Hospital, Florence, Italy, ² Department of Health Sciences, San Paolo Hospital Medical School University of Milan, Milan, Italy, ³ Department of Biomedical, Experimental and Clinical Sciences-Division of Obstetrics and Gynaecology, University of Florence, Florence, Italy, ⁴ Department of Biomedicine, Careggi Hospital, Florence, Italy

* caterinasera79@gmail.com

Abstract

Objective

To investigate the proportion of stillbirths at term associated with abnormal growth using customized birth weight percentiles and to compare histological placental findings both in underweight stillborn fetuses and in live births.

Methods

A retrospective case-control study of 150 singleton term stillbirths. The livebirth control groups included 586 cases of low-risk pregnancies and 153 late fetal growth restriction fetuses. Stillbirths and livebirths from low-risk pregnancies were classified using customized standards for fetal weight at birth, as adequate for gestational age (AGA; 10-90th percentile), small (SGA; <10th percentile) or large for gestational age (LGA; >90th percentile). Placental characteristics in stillbirth were compared with those from livebirths using four categories: inflammation, disruptive, obstructive and adaptive lesions.

Results

There was a higher rate of SGA (26% vs 6%, p<0.001) and LGA fetuses (10.6% vs 5.6%, p<0.05) in the stillbirth group. Among stillbirth fetuses, almost half of the SGA were very low birthweight (<3rd percentile) (12% vs 0.3%, p<0.001). The disruptive (7.3% vs 0.17%; p<0.001), obstructive (54.6% vs 7.5%; p<0.001) and adaptive (46.6% vs 35.8% p<0.001) findings were significantly more common in than in livebirth-low risk. Placental characteristics of AGA and SGA stillbirth were compared with those of AGA and FGR livebirth. In stillbirths-SGA we found a higher number of disruptive (12.8% vs 0%; p<0.001), obstructive (58.9% vs 23.5%; p<0.001) and adaptive lesions (56.4% vs 49%; p 0.47) than in livebirth-FGR.
**Conclusion**

The assessment of fetal weight with customized curves can identify fetuses which have not reached their genetically determined growth potential and are therefore at risk for adverse outcomes. Placental evaluation in stillbirths can reveal chronic histological signs that might be useful to clinical assessment, especially in underweight fetuses.

**Introduction**

Intrauterine fetal death is a most tragic complication of pregnancy, and occurs at an estimated rate of 3.1/1000 deliveries in developed countries and 30/1000 in developing countries. Over 2.6 million stillbirths after 28 weeks of gestation or including fetuses weighting more than 1000g occur each year worldwide and 80% of these occur at the end of pregnancy [1].

Case reviews indicate that many late fetal losses are associated with a failure in identifying risk factors. Underestimating these hazards leads to a lack of appropriate standard of care for pregnancies at risk for stillbirth [2]. Abnormal fetal growth is one of the main risk factors for stillbirth [3]: both small for gestational age (SGA) and large for gestational age (LGA) fetuses have been associated with increased risk of intrauterine death. Among fetuses destined to be stillborn, customized norms, rather than population standards, seem to perform best both in detecting a higher rate of SGA and LGA as well as in identifying SGA fetuses at risk of death [4]. Previous studies have shown that stillbirths are frequently associated with unrecognized growth abnormality [3,5]: if the fetuses fail to reach their growth potential, risk of stillbirth is increased 5 to 10 fold [6].

The placenta is a fundamental substrate for the development and evolution of pregnancy. Placental abnormalities affect several cases of intrauterine fetal death [7] and histological examination is strongly recommended by several international guidelines [8–11] also to interpret unfavorable pregnancy outcomes even in cases apparently occurring without clinical cause. However, despite placental examination appearing to be important in cases of intrauterine fetal death, a recent systematic review failed to identify a specific role of the various placental lesions in stillbirth [12].

We aimed to investigate the proportion of stillbirths at term associated with abnormal growth using customized percentiles for birthweight, and to compare histology of the placentas of underweight stillborn fetuses and two control populations, live born from low-risk pregnancy and live born with late fetal growth restriction (FGR).

**Material and Methods**

This was a retrospective case-control study on all singleton stillbirths delivered between January 2009 and May 2015 in two Tertiary University Hospitals in the North of Italy (Careggi Hospital in Florence and San Paolo Hospital in Milan). The study was exempt from Institutional Review Board approval because placental histology and obstetric and neonatal outcomes were collected as part of clinical management. Patients signed informed consent for the clinical investigations and use of the results for scientific analysis according to privacy laws and human rights.

**Patient selection and data collection**

Inclusion criteria for cases were singleton antepartum fetal death at or after 37 weeks of gestation. Exclusion criteria were major congenital anomalies and/or abnormal karyotype and
maceration at post-mortem evaluation. We defined two control groups. The first included women who attended the low-risk antenatal clinics during the study period, had no relevant obstetric or medical history, and had an uncomplicated pregnancy with a live birth at term. The second control group included pregnancies with late fetal growth restriction (FGR) diagnosed sonographically after 34 weeks during the last year, and monitored until delivery in the Regional Reference Center for high-risk pregnancy, Careggi Hospital, Florence. FGR was defined as any of the following: abdominal circumference <10th percentile, sonographically estimated fetal weight <10th percentile according to Hadlock’s ultrasound norms, or abdominal circumference growth rate <11 mm in a 14-day interval [13]. FGR fetuses were delivered either spontaneously or iatrogenically by induction of labour or caesarean section according to the latest guidelines [14–15].

For each case, clinical data were recorded, including maternal ethnicity, age, parity, level of education, pre-pregnancy body mass index, smoking habits, gestational age at delivery, and birthweight and gender of the neonate.

Each case of stillbirth underwent a thorough evaluation according to a comprehensive protocol as previously published [16,17]. Briefly, the protocol included evaluation of maternal blood pressure, maternal blood testing for inherited and acquired thrombophilia, thyroid function, indirect Coombs test, screening for diabetes, serology for TORCH, placental pathology examination, fetal autopsy, fetal chromosomal analysis (from amniotic fluid or blood or fascia lata sampling). Maternal genital cultures and neonatal swabs were also performed for microbiological analysis.

Evaluation criteria for neonatal fetal weight

Stillbirths and controls were classified on the basis of birthweight using customized percentiles, which included adjustment for maternal pre-pregnancy weight, height, parity and ethnicity as previously reported [5], using the Gestation Related Optimal Weight software (GROW version 6.7.5, 2014, www.gestation.net). The fetal age was the date of delivery for liveborn and stillborn, using menstrual dating criteria or ultrasound criteria when the last menstrual period was unknown, or in case of non-agreement with ultrasound dating (according to the Italian Society of Ultrasound in Obstetrics Guidelines [18]). For stillbirths, excluding macerated fetuses at birth, we considered the birthweight at in the delivery room and not that at the autopsy. Birthweight was considered appropriate for gestational age (AGA) between the 10th and the 90th percentile; the fetuses were otherwise categorized as small for gestational age, SGA (birthweight below 10th percentile) or as large for gestational age, LGA (birthweight above 90th percentile).

Placental samples collection and histological classification

Placental macroscopic inspection of the maternal and fetal plates, umbilical cord and membranes was carried out as previously reported [19]. Placental sampling was conducted according to international criteria [20]. Briefly, after trimming the umbilical cord and membrane, the placental disc was cut in 1 cm thick slices. At least one free membrane roll, one section of the umbilical cord and three conventional full-thickness sections of grossly unremarkable placental parenchyma were sampled for histological examination. All samples were collected by expert fetal and neonatal pathologists using standardized instructions to ensure quality in enrollment sampling and specimen processing. Formalin-fixed paraffin embedded placental tissue samples were processed for histopathological analysis and standard 4 µm thick tissue sections were stained with hematoxylin and eosin and examined at light microscopy by expert pathologists blinded for fetal growth characteristics. Placental lesions were identified through
microscopy study according to standard international references [21,22]. Histological placental findings were classified as previously reported using four categories [23,24]: lesions of inflammation, disruptive lesions, obstructive lesions and adaptive lesions (Table 1).

**Statistical analysis**

For categorical variables, frequencies and percentages were reported, means and standard deviations (±SD) for continuous variables. Differences between groups were analyzed with Student’s t test, Fisher exact test or chi-square test when appropriate. An a priori two-tailed level of significance was set at the 0.05 level.

**Results**

There were 165 term stillbirths during the period of the study, of which 15 fetuses were excluded because of maceration, leaving 150 to be included in the study group. Two control groups were included:

- 586 livebirths from 600 low-risk uneventful singleton term pregnancies monitored at two low-risk clinics during the same period (14 cases were excluded due to incomplete data).
- 153 livebirth cases of late FGR diagnosed sonographically after 34 weeks during the last year.

Patient characteristics are summarized in Table 2.

| Table 1. Patterns of histologic findings. |
|-----------------------------------------|
| **Inflammation lesions**                |
| Severe Acute Chorioamnionitis            |
| Funisitis                                |
| Villitis of unknown etiology             |
| **Disruptive lesions**                  |
| Abruptio placenta                        |
| Rupture of vasa praevia                  |
| Feto-maternal haemorrhage                |
| **Obstructive lesions**                 |
| Infarction (>20% of the parenchyma)      |
| Massive fibrin deposition                |
| Diffuse villous edema                    |
| Decidual vasculopathy                    |
| Fetal thrombotic vasculopathy            |
| **Adaptive lesions**                    |
| Incremented syncytial knots              |
| Chorangiosis                             |
| Vilous branching anomalies               |

doi:10.1371/journal.pone.0166514.t001

Gestational age did not significantly differ in all groups (38.5±1.3 vs 39.4±1.2 vs 39.3±1.72). Birthweight was lower in the livebirth-FGR than the stillbirth and livebirth-low risk groups (2507.27±329.15 vs 3330±314.3 in livebirth-low risk vs 3047±577.8 in stillbirth; p<0.001).

The rate of neonatal gender was not significantly different in the three groups. In the stillbirth group, fetal growth was classified as abnormal (<10th or >90th percentiles) in 55 (36.6%) and
normal in 95 (63.4%) of the cases. Distribution of growth percentiles in the stillbirth population is shown in Fig 1.

Customized percentiles show a U-shaped distribution with increased proportions of SGA, especially ≤3˚ percentile, and LGA fetuses. Customized percentiles identified a higher rate of SGA and LGA in the stillbirths compared to the livebirth-low risk group, with 26% of stillbirths vs 6% of livebirth being SGA (p < 0.001). Almost half of these had a very low birthweight (≤3˚ percentile) (12% vs 0.3%, p < 0.001). Moreover, in the stillbirth group we found a double rate of LGA fetuses (10.6% vs 5.6%, p < 0.05). SGA pregnancies were associated with a 5.5-fold increased risk of stillbirth compared to AGA using customized standards and severe SGA (birthweight ≤3˚ percentile) was associated with a 39-fold increased risk of death. LGA fetuses were associated with a 1.99-fold increased risk of stillbirth at term using customized curves.

Placental characteristics are summarized in Table 4.

Histological findings are not mutually exclusive, more than one lesion may coexist in each case.

Table 3. Neonatal characteristics.

| Main characteristics                        | Stillbirth (n. 150) | Livebirth-low risk (n. 586) | Livebirths FGR (n.153) | p1 value | p2 value | p3 value |
|---------------------------------------------|---------------------|-----------------------------|-------------------------|----------|----------|----------|
| Gestational age at delivery (weeks)         | 38.5 ±1.3           | 39.4±1.2                    | 39.3±1.72               | n.s      | n.s      | n.s      |
| GA > 40 weeks                               | (14) 9.3%           | (235) 40.1%                 | (47) 30.7%              | <0.001   | <0.001   | <0.05    |
| Neonatal birthweight (grams)                | 3047 ±577.8         | 3330 ±314.3                 | 2507.27±329.15          | <0.001   | <0.001   | <0.001   |
| AGA according to customized centiles        | (95) 63.4%          | (518) 88.4%                 | -                       | <0.001   | -        | -        |
| SGA according to customized centiles        | (39) 26%            | (35) 6.0%                   | (153) 100%              | <0.001   | <0.001   | <0.001   |
| Severe SGA (Birthweight ≤3˚ percentile)      | (18)12%             | (2) 0.3%                    | (84) 54.2%              | <0.001   | <0.001   | <0.001   |
| LGA according to customized centiles        | (16) 10.6%          | (33) 5.6%                   | -                       | <0.05    | -        | -        |
| Neonatal gender: Male                       | (77) 51.3%          | (304) 51.9%                 | (68) 44.4%              | n.s      | n.s      | n.s      |
| Neonatal gender: Female                     | (73) 48.7%          | (282) 48.1%                 | (85) 55.6%              | n.s      | n.s      | n.s      |

P1: stillbirth vs livebirth from low-risk pregnancy; P2: stillbirth vs livebirth with late FGR; P3: livebirth from low-risk pregnancy vs livebirth with late FGR
Placental lesions occurred more frequently in the stillbirth than the livebirth-low risk group: disruptive (7.3% vs 0.17%; p < 0.001), obstructive (54.6% vs 7.5%; p < 0.001) and also adaptive (46.6% vs 35.8%; p < 0.001) findings were significantly more common for stillbirths, regardless of birthweight percentile.

To investigate the relationship between abnormal fetal weight and stillbirth, we subdivided the stillbirth population in AGA or SGA subgroups and we compared their placental characteristics with those of livebirth-AGA and livebirth-FGR (Table 5).

The highest incidence of disruptive (12.8% vs 0.17%; p < 0.001), obstructive (58.9% vs 7.5%; p < 0.001), and adaptive (56.4% vs 35.8%; p < 0.001) lesions occurred in stillbirth-SGA. Moreover, in stillbirth-SGA we found a higher number of disruptive (12.8% vs 0%; p < 0.001), obstructive (58.9% vs 23.5%; p < 0.001) and adaptive lesions (56.4% vs 49%; p 0.47) than in livebirth-FGR.

Table 4. Placental characteristics in cases and controls.

| Placental lesions | Stillbirth (n. 150) | Livebirth-Low risk (n.586) | Livebirth-FGR (n.153) | p1 value | p2 value | p3 value |
|------------------|---------------------|---------------------------|-----------------------|----------|----------|----------|
| Inflammatory     | (11) 7.3%           | (29) 4.9%                 | (16) 10.4%            | n.s.     | n.s.     | <0.05    |
| Disruptive       | (11) 7.3%           | (1) 0.17%                 | (0) 0%                | <0.001   | <0.05    | n.s.     |
| Obstructive      | (82) 54.6%          | (44) 7.5%                 | (36) 23.5%            | <0.001   | <0.001   | <0.001   |
| Adaptive         | (70) 46.6%          | (210) 35.8%               | (75) 49%              | <0.05    | n.s.     | <0.05    |

p1: stillbirth vs livebirth from low-risk pregnancy; p2: stillbirth vs livebirth with late FGR; p3: livebirth from low-risk pregnancy vs livebirth with late FGR.

doi:10.1371/journal.pone.0166514.t004
Comparing the livebirth-FGR and livebirth-AGA groups, obstructive (23.5% vs 3.6%; p<0.001) and adaptive lesions (49% vs 34.9%; p<0.001) were still significantly higher in livebirth-FGR but lower than in stillbirth-SGA. Interestingly, comparing stillbirth-SGA and livebirth-FGR, both ≤3° customized percentile, there was a significant difference in the rate of obstructive lesions (88.2% vs 21% vs 3.6%) with livebirth-AGA.

While the ratio of obstructive and adaptive lesions for livebirth-AGA was one to ten (3.6 vs 34.9%), in unfavorable conditions, such as severe SGA or FGR, the ratio changes. In cases of severe-FGR the ratio drops to 1 to 2 (21.8% vs 40.6%) and conversely the ratio is reversed in cases of stillbirth with severe-SGA, reaching 4 to 1 (88.2% vs 23.5%) (Fig 2).

**Discussion**

This is, to our knowledge, the first study that looked at a cohort of stillbirths and compared their characteristics and placental histopathology with two control groups. Fetal growth restriction, and small for gestational age as its proxy, has the strongest association with stillbirth [25]. Our study confirmed a significant relationship between SGA and risk of intrauterine death at term.

| Placental lesions | Stillbirth-AGA (n. 95) | Stillbirth-SGA (n.39) | Livebirth-AGA(n.518) | Livebirth-FGR (n.153) | p1 value | p2 value | p3 value |
|-------------------|------------------------|-----------------------|----------------------|-----------------------|----------|----------|----------|
| Inflammatory      | (10) 10.5%             | (3) 7.7%              | (24) 4.6%            | (16) 10.4%            | <0.05    | n.s.     | <0.05    |
| Disruptive        | (5) 5.2%               | (5) 12.8%             | (0) 0%               | (0) 0%                | <0.001   | <0.05    | n.s.     |
| Obstructive       | (44) 46.3%             | (23) 58.9%            | (19) 3.6%            | (36) 23.5%            | <0.001   | <0.001   | <0.001   |
| Adaptive          | (9) 9.4%               | (22) 56.4%            | (181) 34.9%          | (75) 49%              | <0.001   | <0.001   | <0.001   |

p1: stillbirth-AGA vs livebirth-AGA; p2: stillbirth-AGA vs livebirth with late FGR; p3: stillbirth-SGA vs livebirth with late FGR.

do:10.1371/journal.pone.0166514.t005

![Fig 2. Distribution of obstructive and adaptive placental alterations in the groups.](doi:10.1371/journal.pone.0166514.g002)
Although some risk factors for stillbirth have been identified, the main cause of stillbirth often remains elusive. Previous studies suggest that advanced maternal age is a risk factor for stillbirth [26] but in our study we do not report any significant difference between the groups. Other maternal factors like nulliparity, smoking status, pre-pregnancy BMI and obesity were all statistically significant, confirming data from other studies [25]. Concerning fetal risk factors, stillbirth is strongly related to impaired fetal growth, so both growth restriction and excess growth are risk factors for death during pregnancy [3], therefore obstetrical care should focus on both SGA and LGA pregnancies.

One challenge for our study was that it could only be conducted retrospectively: in fact, if during pregnancy we had noticed any fetuses at risk for adverse outcomes we would have changed the timing of delivery to prevent intrauterine death. In the absence of prospective information about fetal growth, the use of customized percentiles allowed us to determine retrospectively that many of these babies had failed to reach their growth potential. In previous work we have shown, using ROC curves, that customized standards identified a higher percentage of FGR in all cases of fetal death occurring after the 28th week; 26% of stillbirths occurring in the third trimester of pregnancy were reclassified as FGR by customized growth curves [5].

An impaired placenta might become the limiting element of fetal growth. The fetus and the placenta constitute a single morpho-functional unit and must be analyzed in their ensemble. In case of poor fetal-neonatal outcomes, placental histology allows a better understanding of the pathophysiology of adverse outcomes, and provides useful information for medicolegal considerations and for the management of subsequent pregnancies.

In a review of 104 perinatal deaths, placental examination by itself could identify the cause of fetal death in 48% to 51% of cases, and placental findings could explain the cause of death in 69% of stillbirth cases [27]. These findings coincide with other reviews reporting 35% to 88% of stillbirth cases having placental findings causative of death [28]. In this study we focused on stillborn cases with a post-natal diagnosis of abnormally low fetal weight; the objective was to analyze placental characteristics, to explore if small for gestational age stillborn fetuses exhibited particular placental lesions. Comparing live-born babies from pregnancy affected by FGR and live-born from low-risk pregnancy with stillbirth, we observed an increased rate of placental lesions in stillborn cases, 14.6% vs 5.1% vs 1.9% in those with growth failure.

Obstructive lesions seem to be the main conditions associated to low fetal weight in our stillborn cases; in fact, they were present in 54.6% of all stillbirths and 58.9% of SGA/stillbirths, while only in 7.5% of live births from low-risk pregnancy and in 23.5% of late FGR livebirths. This finding suggests that these placental abnormalities may play a crucial role. Also the relationship between obstructive lesions and adaptive lesions have a predominant function in the placentas of stillborn and liveborn with growth failure. We found adaptive lesions in more than half of SGA/stillbirths, in 49% of FGR livebirths and also in 35.8% of placentas from low-risk pregnancy. Moreover, our results show that the ratio of obstructive/adaptive lesions, and not the absolute rate of one type of these histological findings, strongly connected to adverse outcome. Chorionic villi adapt their development on the basis of environmental conditions. During chronic hypoxia placental villi could develop a heterogeneous pattern, showing accelerated maturity, small size and focal hypervascularity (chorangiosis) [29].

Unfortunately we still do not know what kind of injury plays a principal role in the placental dysfunction affecting fetal growth. In our study it is clear that obstructive lesions have a predominant role but if the placenta develops adaptive and compensatory mechanisms this can allow the fetus to survive. This hypothesis can be supported by detecting the highest number of obstructive findings in absence of an adequate number of adaptive lesions when we compare AGA stillbirths with AGA live births. Therefore the identification of this placental pattern in
cases of abnormal pregnancy outcome could provide valuable information on the etiopathogenesis of the adverse event [30].

In conclusion, our study compares a population of stillbirths with live births after FGR during pregnancy, and healthy fetuses after uneventful pregnancies, analyzing the differences in placental characteristics. We confirm that several cases of stillbirth may occur in pregnancies unexpectedly affected by intrauterine growth restriction and that customized curves are the best method to assess, even retrospectively, whether a fetus has reached its growth potential. We found that placental evaluation can reveal chronic histological signs that might help to understand the pathophysiology leading to the unfavorable outcome.

Supporting Information
S1 Table. Placental characteristics in AGA and SGA stillbirth vs AGA and SGA livebirth. (DOCX)

Acknowledgments
Thanks to Ms Stacey Enersen, a native English speaker, who edited the manuscript.

Author Contributions
Conceptualization: FM GB.
Data curation: CS MC EB SS.
Formal analysis: CS LA MC.
Investigation: EB FC GT.
Methodology: FM GS LA.
Project administration: FM.
Resources: CS.
Software: EB.
Supervision: FM.
Validation: SS MR.
Visualization: FM LA.
Writing – original draft: FM MC CS LA SS.
Writing – review & editing: FM CS MC LA SS.

References
1. Fretts R. Stillbirth epidemiology, risk factors, and opportunities for stillbirth prevention. Clin Obstet Gynecol. 2010; 53(3):588–596. doi: 10.1097/GRF.0b013e3181eb63fc PMID: 20661043
2. Gardosi J, Giddings S, Buller S, Southam M, Williams M. Preventing stillbirths through improved antenatal recognition of pregnancies at risk due to fetal growth restriction. Public health. 2014; 128:698–702. doi: 10.1016/j.puhe.2014.06.022 PMID: 25151298
3. Bukowski R, Hansen NI, Willinger M, Reddy UM, Parker CB, Pinar H, et al. Fetal Growth and Risk of Stillbirth: A Population-Based Case—Control Study. A Population-Based Case—Control Study. PLoS Med. 2014; 11(4): e1001633. doi: 10.1371/journal.pmed.1001633 PMID: 24755550
Monari F, Alberico S, Avagliano L, Cetin I, Cozzoli no S, Gargano G, et al. Relation between maternal... growth restriction. The Journal of Maternal-Fetal and Neonatal Medicine. 2012; 26(1):16–20. doi: 10.3109/14767058.2012.718399 PMID: 22882114

Claussen B, Gardosi J, Francis A, Cnattingius S. Perinatal outcome in SGA birth defined by customised... birthlessness. BJOG. 2001; 108: 830–4. PMID: 11510708

Korteweg FJ, Erwich JJ, Holm JP, Ravisé JM, van der Meer J, Veeger NJ et al. Diverse placental... as the main causes of fetal death. Obstet Gynecol. 2009; 114:809–17. doi: 10.1097/AOG.0b013e1817b7e2be PMID: 19888039

Royal College of Obstetricians and Gynaecologists, Green-Top Guideline 55-Late Intrauterine Fetal Death and Stillbirth. London: Royal College of Obstetricians and Gynaecologists; 2010.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 102: management of stillbirth. Obstet Gynecol 2009; 113(3):748e61.

Flenady V. PSANZ Clin Pract Guidel Perinat Mortal Version 2.2; 2009.

SOGC clinical practice guideline. Stillbirth investigation and bereavement: guideline for stillbirth investigation. Number 178, June 2006. J Obstet Gynaecol Can; 2006; 28:540–5

Placek I, Sebire NJ, Man JA, Brownbill P, Heazell AEP. Systematic review of placental pathology reported in association with stillbirth. Placenta. 2014; 35: 552–62 doi: 10.1016/j.placenta.2014.05.011 PMID: 24953162

Divon MY, Chamberlain PF, Sipos L, Manning FA, Platt LD. Identification of the small for gestational... of birth: the role of maternal prepregnancy body mass index. J Matern Fetal Neonatal Med. 2012; 25(10):1197–201 PMID: 2338875

Seravalli V, Baschat AA. A uniform management approach to optimize outcome in fetal growth restriction. Obstet Gynecol Clin North Am. 2015 Jun; 42(2):275–88 doi: 10.1016/j.ogc.2015.01.005 PMID: 26002166

Figueiras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther. 2014; 36(2):86–98. doi: 10.1159/000357592 PMID: 24457811

Avaglano L, Marconi AM, Romagnoli S, Bufamante GP. Abnormal spiral arteries modification in stillbirths: the role of maternal prepregnancy body mass index. J Matern Fetal Neonatal Med. 2012; 25(12):2789–92. doi: 10.3109/14767058.2012.705395 PMID: 22746325

Monari F, Alberico S, Avagliano L, Cetin I, Cozzolino S, Gargano G, et al. Relation between maternal thrombophilia and stillbirth according to causes/associated conditions of death. Early Hum Dev. 2012; 88(4):251–4. doi: 10.1016/j.earlhumdev.2011.06.013 PMID: 21945103

Ultrasound Guidelines SIEOG 2015, the Italian Society of Ultrasound in Obstetrics Guidelines

Avagliano L, Marconi AM, Candiani M, Barbera A, Bufamante G. Thrombosis of the umbilical vessels revisited. An observational study of 317 consecutive autopsies at a single institution. Hum Pathol. 2010; 41(7):971–8. doi: 10.1016/j. Humpath.2009.07.026 PMID: 20236685

Langston C, Kaplan C, Macpherson T, Manci E, Peevy K, Clark B et al. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med. 1997 May; 121(5):449–76. PMID: 9167599

Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C; Society for Pediatric Pathology, Perinatal Section, Amniotic Fluid Infection Nosology Committee. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2003; 6(5):435–48. doi: 10.1016/s1002-4003-003-0070-7 PMID: 15547172

Redline RW, Ariel I, Baergen RN, Desa DJ, Kraus FT, Roberts DJ et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2000; 3(5):435–48. doi: 10.1016/s1002-4003-003-0056-x PMID: 11070037

Avaglano L, Danti L, Doi P, Felis S, Guala M, Locatelli A et al. Autophagy in placentas from acidotic newborns: an immunohistochemical study of LC3 expression. Placenta. 2013; 34(11):1081–4. doi: 10.1016/j.placenta.2013.09.004 PMID: 24070620

Avaglano L, Locatelli A, Danti L, Felis S, Mecacci F, Bufamante GP. Placental histology in clinically unexpected severe fetal acidemia at term. Early Hum Dev. 2015 May; 91(5):339–43 doi: 10.1016/j.earlhumdev.2015.03.004 PMID: 25875757

Gardosi J, Madurasinge V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ. 2013 Jan 24; 346:f108. doi: 10.1136/bmj.f108 PMID: 23349424
26. Waldenström U, Cnattingius S, Norman M, Schytt E. Advanced Maternal Age and Stillbirth Risk in Nulliparous and Parous Women. Obstet Gynecol. 2015; 126(2):355–62. doi: 10.1097/AOG.0000000000000947 PMID: 26241426

27. Tellefsen CH, Vogt C. How important is placental examination in cases of perinatal deaths? Pediatr Dev Pathol. 2011; 14(2):99–104 doi: 10.2350/10-07-0870-OA.1 PMID: 20718631

28. Kidron D, Bernheim J, Aviram R. Placental findings contributing to fetal death, a study of 120 stillbirths between 23 and 40 weeks gestation. Placenta. 2009; 30:700–704. doi: 10.1016/j.placenta.2009.05.009 PMID: 19535137

29. Stanek J. Hypoxic Patterns of Placental Injury. A Review. Arch Pathol Lab Med. 2013; 137:706–20. doi: 10.5858/arpa.2011-0645-RA PMID: 23627456

30. Stanek J. Utility of diagnosing various histological patterns of diffuse chronic hypoxic placental injury. Pediatr Dev Pathol. 2012; 15(1):13–23. doi: 10.2350/11-03-1000-OA.1 PMID: 21864121