Stillbirth and intrauterine fetal death: factors affecting determination of cause of death at autopsy

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+A: Abstract

Objectives There have been many attempts to classify cause of death in stillbirth, all such systems being subjective, allowing for significant observer bias, making accurate comparisons between systems challenging. The aim of this study was to examine factors relating to determination of cause of death by using a large dataset from two specialist centres, in which observer bias has been reduced by objectively classifying findings and assigning causes of death based on predetermined criteria.

Methods Detailed autopsy reports from intrauterine fetal deaths (IUFD) during 2005-2013 in the second and third trimesters were reviewed and findings entered into a specially designed database, in which cause of death (CoD) was assigned using predefined objective criteria. Data regarding CoD categories and factors affecting determination of CoD were analysed through queries and statistical tests run using Microsoft Access, Excel, Graph Pad Prism and StatsDirect, with Mann–Whitney *U*-test and comparison of proportions testing as appropriate.

Results There were 1,064 IUFDs, including 639 stillbirths at >23 weeks' gestation. Overall, around 40% (412 (39%)), had a definite or highly likely cause of death identified, whilst 60% (652) were classified as 'unexplained'. Of these, around half had identified risk factors, or lesions of uncertain significance present, whilst the remaining half (292 (45%)) were entirely unexplained. A stepwise increase in the proportion of unexplained deaths was observed with increasing severity of maceration. Black and Asian women had significantly greater proportions of deaths due to ascending infection whilst women aged over 40 had significantly increased placental-related causes of death. There was no significant difference in cause of death distribution by maternal

body mass index or with increasing post-mortem interval. Almost 20% of definitive or likely causes of death could be identified from clinical review or external examination / imaging of the fetus, with most of the remainder being determined following placental examination.

Conclusions Based on objective criteria, most IUFDs across gestation remain unexplained despite autopsy examination. The rate of unexplained death varies between 30 and 60% depending on interpretation of the significance of features. The cause of death provided across studies is variable and dependent on both the classification system used and subjective interpretation such that reduction in the proportion of 'unexplained' cases across studies is largely based on speculation around mechanism of death. Novel methods to determine objectively the mechanism of death at postmortem examination are required.

+A: Introduction

The primary aim of postmortem investigation of intrauterine death is determination of cause and mechanism of death, to facilitate counseling of parents, management of subsequent pregnancies and future interventions[1–4]. Over the last 50 years there have been many attempts to classify cause of death in stillbirths, but, depending on which of the more than 30 classification systems[5] is used, a varying but significant proportion (15–60%) of stillbirths remain unexplained, despite postmortem examinations being undertaken in specialist centers[6,7]. Classification systems include the Aberdeen[8,9], based predominantly on obstetric findings and clinical history, the Wigglesworth[6], which subdivides cases into general groups, the Relevant Condition at Death (ReCoDe)[7], which records associated risk factors, and the Causes of Death and Associated Conditions (CODAC)[10], which is designed to accommodate main cause of death and associated conditions (the latter two systems recording apparent growth restriction as a specific cause of stillbirth based on varying criteria).

Each system has advantages and disadvantages and no perfect system exists, the major consideration being the underlying purpose for which the data will be used. A review of classification systems reported that the best performing, in terms of ease of use, interobserver agreement and lowest rate of 'unexplained' deaths was CODAC[11]. However, all such systems, especially when based on population or registry data, are subjective, thus allowing for observer bias and making accurate comparisons between systems challenging. There are several explanations for the differences in reported frequencies of 'unexplained' stillbirths, including that classification systems may record events that were not causally related to the stillbirth. Whilst it is tempting to suggest that

reducing unexplained cases is beneficial, this is only true if there is definitive evidence that the 'cause' assigned is correct; in practice, the significance of factors in individual cases can be difficult to assess.

The aims of this study are therefore to examine factors relating to determination of cause of death using a large dataset extracted from an autopsy research database including cases from two specialist centers, in which observer bias was reduced as far as possible by recording objectively findings at autopsy and assigning causes and classifications of death based on predetermined criteria..

+A: Methods

This analysis was part of a larger study examining autopsy findings in intrauterine deaths, in which detailed autopsy reports from deaths during the second and third trimesters were reviewed and findings entered into a specially designed Microsoft Access (Microsoft Corp., Redmond, WA, USA) autopsy database. Cases were from 2005 to 2013 inclusive from Great Ormond Street Hospital and St George's Hospital, London. Clinical details, autopsy findings and results of ancillary investigations were recorded (> 400 variables per case) based on predefined criteria documented in the Database Manual (Appendix S1). Intrauterine fetal deaths (IUFDs) occurring ≤ 23 weeks' gestation were recorded as second-trimester IUFDs, while those ≥ 24 weeks' gestation were classified as stillbirths. Data were analyzed through queries and statistical tests run using Microsoft Access and Microsoft Excel (Microsoft Corp.), GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA) and Stats Direct (StatsDirect Ltd., Altrincham, UK). $P < 0.05$ was considered statistically significant.

For the purposes of this study, strict predetermined criteria were used to assign an objective cause of death for each case. Cause of death was based on definite documented findings, including clinical history, macroscopic and microscopic features and results of ancillary investigations, rather than the subjective opinion of the initial reporting pathologist. For example, 'abruption' was defined as a definite history of clinical abruption with or without concurrent placental or autopsy findings; 'ascending infection' was histologically proven chorioamnionitis with or without funisitis with or without fetal pneumonia; 'birth trauma' was a documented complication that occurred during delivery leading to fatal intrapartum event, with consistent autopsy findings; 'congenital abnormality' was a congenital abnormality documented at autopsy, which likely accounted for the death; 'cord accident' was a witnessed and recorded cord complication during delivery, such as cord prolapse (the isolated postmortem finding of changes such as cord knot or abnormal coiling at autopsy in the absence of specific clinical history or other findings was not considered a definite cause of death); 'placental' was significant and definite abnormal placental pathological findings present which likely caused the death, e.g. severe maternal vascular malperfusion, chronic histiocytic intervillositis (placental histological changes of uncertain clinical significance such as mild changes suggestive of impaired maternal vascular perfusion, low-grade villitis of unknown etiology and intervillous thrombi, and non-specific cord changes such as coiling index, were not included in this category). In cases in which no definitive cause of death was identified, the case was classified, for the purposes of this study, as 'unexplained'. However, in order to allow further analysis, these cases were further subclassified as follows: 'unexplained lesion, fetus' was defined as an unexplained cause of death, but in the presence of a fetal finding of unknown

significance (e.g. mild intraventricular hemorrhage only); ‘unexplained lesion, clinical’ was in the presence of a clinical risk factor known to increase stillbirth risk but of unknown significance in the specific case (e.g. maternal cholestasis or diabetes mellitus); ‘unexplained lesion, cord’ was in the presence of a cord finding of unknown significance (e.g. true cord knot but with no thrombosis or other pathological findings); ‘unexplained lesion, placenta’ was in the presence of placental findings of unknown significance (e.g. villous changes such as increased syncytial knots, but without changes of severe malperfusion such as infarcts or vasculopathy or intervillous thrombi); ‘unexplained obese’ was in association with documented maternal obesity (BMI>30); ‘unexplained, post-term’ was in association with documented post-term delivery (post 41 weeks); ‘unexplained with previous fetal loss’ was in association with maternal history of previous fetal loss; ‘unexplained with diabetes’ was in association with diabetes mellitus or gestational diabetes; ‘unexplained, unexplained’ was no cause of death found at autopsy, no abnormal placental findings and no clinical risk factor associations; ‘unexplained all’ was no cause of death found based on antenatal history and autopsy findings; this category encompassed all of the ‘unexplained’ groups listed above. If any specific cause of death was present, this was used to classify the case, even in the presence of underlying maternal issues such as obesity or diabetes mellitus.

The total dataset comprised 1064 intrauterine deaths across both second and third trimesters, including 425 IUFDs $\leq$ 23 weeks’ gestation (246 early (< 20 weeks’ gestation) and 179 late (20–23 weeks)) and 639 stillbirths $\geq$ 24 weeks; the classification of final cause of death for the overall group and according to gestational age groups is

provided in Table 1 and Figures S1 and S2. Overall, around 40% of cases were associated with a definite or highly likely cause of death, based on clear clinical history and/or abnormal pathological findings at autopsy.

Approximately two thirds of cases, however, did not have a clear cause of death identified and hence were 'unexplained'. Of these, around half either had identified risk factors, such as diabetes mellitus, or lesions of uncertain significance, whilst the remainder had no abnormal features and were entirely unexplained. For the purposes of this study, FGR IUGR was given as the cause of death either for cases in which an antenatal diagnosis of IUGR was documented and in which surveillance was ongoing, or for cases in which placental pathology of maternal vascular malperfusion or other definitive FGR-associated pathology was identified, such cases being classified as 'placental'. The issue of determination of FGR based on body weight and organ weight ratios is investigated in detail elsewhere[12–16].

'Unexplained' cases represented the largest category regardless of gestational age. Placental causes of death, such as placental abruption, placental abnormalities and unexplained cases with placental lesions were significantly more common in stillbirths compared with IUFDs ($z = 2.4$, $P = 0.02$; $z = 5.1$, $P < 0.0001$; and $z = 2.4$, $P = 0.019$, respectively). Ascending infection and unexplained death with a history of fetal loss were significantly more common in second trimester IUFDs than in stillbirths ($z = 7.8$, $P < 0.0001$; and $z = 4.1$, $P < 0.0001$, respectively). No other cause of death categories had significant differences between gestational-age groups.

There were 81 cases with some form of 'limited' autopsy based on parental consent (52 with only external examination with postmortem cross-sectional imaging

and placental examination only; 22 with standard autopsy but limited to specific body cavities; and seven with only postmortem imaging followed by organ sampling only. Of these limited examinations, 51 (63%) were unexplained, a proportion not significantly different from the overall percentage of unexplained deaths (62%); thus for the analysis all autopsies were reported as one group.

The majority of cases were unexplained across all ethnic groups, but Black and Asian mothers had significantly greater proportions of deaths due to ascending infection (Table 2, Figure S3; $z = 7.4$, $P < 0.0001$ and $z = 2.4$, $P = 0.08$, respectively). The majority of the study population (77%) had a maternal age ≤ 35 years with the majority of deaths being unexplained regardless of maternal age group ’and the most common cause of death category remained unexplained (Table 3, Figure S4) (not significantly different between age groups, $z = 1.27$, $P = 0.21$). However, mothers over the age of 40 had a significantly increased frequency of placental causes of death ($z = 2.33$, $P = 0.02$). There was no significant difference in cause of death distribution according to maternal body mass index (BMI); in particular, unexplained deaths had similar frequencies regardless of maternal BMI category (Table 4, Figure S5, $z = 0.73$, $P = 0.46$).

Fetuses with unexplained deaths were significantly more macerated than were those with other causes of death ($z = 9.24$, $P < 0.0001$) and there was a stepwise increase in the proportion of unexplained deaths with increasing severity of maceration. (Table 5, Figure S6); even when cases of ascending infection were excluded from the analysis, cases with unexplained deaths were significantly more macerated than were those with other causes of death ($z = 3.4$, $P < 0.0001$). There was no significant effect of postmortem interval (PMI, time interval from delivery to postmortem examination)

on determination of cause of death (Table 6, Figure S7), with unexplained cases being similar at all intervals (z = 0.48, P = 0.63). Finally, when using predetermined objective criteria to determine cause of death, there was no significant effect of the pathologist performing the autopsy (Figure S8), the proportion of unexplained cases being similar across all pathologists (X^2=3.28, P = 0.06).

In order to compare our findings with published data, we applied the ReCoDe classification system, using calculations of unadjusted birth-weight centile to determine the proportion of cases that were small-for-gestational age (SGA, < 10th centile of the normal liveborn range). These cases were coded 'A7 – Fetal Growth Restriction' together with those cases diagnosed with antenatal IUGR. (SGA cases could only be calculated for fetuses >23 weeks of gestation with documented birth weight, so the total number of cases that could be classified using the ReCoDe system was 529). Using this classification system, 37% of deaths were SGA (similar to the 43% previously reported)[7].

Around 20% of all deaths could be classified based primarily on the antenatal history, clinical events, antenatal ultrasound scan findings or external examination (for example, congenital anomalies, documented acute placental abruption). Placental histological examination identified the cause of death in a further 18% cases. The invasive autopsy examination with associated organ sampling only provided the specific cause of death in around 1% of cases. The remainder of the deaths in the study population were unexplained, with invasive examination providing limited additional diagnostic information (Figure S9).

+A: Discussion

The findings of this study present important conclusions for both clinical practice and epidemiological research studies in stillbirth and IUFD. First, based on objective criteria, the majority of intrauterine deaths remain unexplained regardless of gestational age, despite full autopsy examination by specialist pathologists. Second, the rate of unexplained death may vary from around 30% to 60% depending on the interpretation of, and the significance attributed to, clinical history, autopsy and placental examination findings, despite actual features being similar. Third, the cause of death provided both clinically and in population-based studies is variable and highly dependent on the classification system used; reduction in the proportion of 'unexplained' cases across studies may be based on speculation regarding mechanisms of death. Finally, maceration changes which occur after death are associated with decreased frequency of identification of specific cause of death at autopsy but there is no effect of increasing interval between delivery and postmortem examination on determination of the cause of death.

Based on predefined criteria, around 60% of intrauterine deaths had an unexplained cause, despite autopsy examination being performed; around half of these were associated with no clinical, fetal or placental lesions, being entirely unexplained, while the remainder showed either associated risk factors or findings of uncertain significance. These proportions are largely in keeping with those of most other studies and highlight that, depending on which classification system is used, one to two thirds of stillbirths are unexplained based on whether the classifiers interpret features to be sufficient for cause of death[17]. These data, using a predefined, objective hierarchical

classification, suggest that differences in cause of death reported across studies, centers and classification systems are likely related to differences in subjective interpretation of findings rather than differences in objective findings at autopsy. In this study, strict criteria were used regarding cause of death (both regarding FGR as cause of death and interpretation of placental findings; for example, isolated cord features, such as possible abnormal coiling, were not regarded as a cause of death). This strict approach allowed objectivity and consistency but likely explains the relatively high frequency of apparent unexplained cases compared with historical studies based on clinical reports. Until objective novel laboratory criteria are available to determine or confirm specific mechanisms of death, these issues cannot be resolved.

The second commonest cause of death overall was ascending infection, representing 17% of the total population, similar to that reported in other studies[18–20]. One previous study reported that the rate of chorioamnionitis, both preterm and term, increased in all ethnicities over a 15-year period, with Caucasian mothers having a lower relative risk than other ethnicities[21]. The present data confirm that Black and Asian mothers have a significantly greater proportion of deaths associated with ascending infection and that ascending infection is a major cause of non-macerated late second-trimester IUFD. In general, other demographic factors, such as maternal age and obesity, showed little association with specific causes of IUFD, other than there being a significantly greater frequency of placental pathologies in mothers over 40 years of age. There are few comparable published data regarding maternal demographic factors and specific causes of stillbirth; one study examined national stillbirth data and suggested an increased risk of term stillbirth among mothers ≥ 35 years of age due to

major fetal congenital abnormalities, maternal medical disorders and obstetric mechanical causes[22].

There was an association between maceration, indicating an extended intrauterine interval between death and delivery, and apparently unexplained death. A relationship between proportion of unexplained deaths and worsening maceration was noted, suggesting a possible effect on the ability to identify the cause of death at autopsy. One confounding factor could be ascending infection, since this leads to onset of labor with intrapartum death of a non-macerated fetus. However, this does not account for the effect, since the association remained even once ascending infection was excluded, suggesting a genuine effect of maceration. There was no association between postmortem interval and determination of cause of death, demonstrating that delay between delivery and autopsy, even of many days, does not affect the likelihood of determining a cause of death, providing that bodies are refrigerated suitably; this factor should not affect decisions regarding investigation after death.

In order to allow comparison with published data, cases were classified using ReCoDe; this resulted in many more deaths becoming attributed to FGR (37%), based purely on fetal weight at delivery (although there are flaws with this approach). Nevertheless, around one third of cases remained unexplained even using ReCoDe. These findings demonstrate the difficulty in comparing data across classification systems even when the same dataset is being assessed, due to the arbitrary, subjective nature of categorization and difficulty in interpretation of the significance of factors in an individual case[7].

Around 20% of causes of death could have been identified from careful clinical review or fetal external examination/imaging and placental examination; traditional invasive autopsy examination itself only identifed the cause in a minority of cases, most remaining unexplained if the placental findings and clinical history were non-contributory. Hence, most published data, which include a composite of all aspects of the postmortem examination, overestimate the role of internal examination and sampling, although such examination may provide supportive evidence for a given diagnosis. These findings suggest that the most important aspects of stillbirth investigation include clinical review, external examination and/or imaging for structural abnormalities, and specialist placental examination; these should be encouraged in all cases, especially since, at present, only around half of parents in the UK accept standard autopsy.

Regardless of the exact proportion, dependent on interpretation and classification as discussed above, the most important implication of this study for clinical practice is that the mechanism of intrauterine death in many cases remains unexplained. We need to develop effective methods to identify risk-factors for intrauterine death antenatally and to determine reliably and objectively the mechanism of death in individual cases at postmortem. This necessitates changes in investigative methods, with development of novel laboratory approaches to provide reliable, acceptable and objective evidence for the underlying pathological processes leading to intrauterine death.

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The following supporting information may be found in the online version of this article:

Appendix S1 Database manual

Figure S1

Figure S2

Figure S3

Figure S4

Figure S5

Figure S6

Figure S7

Figure S8

Table 1 Simplifed cause of death, defined objectively based on autopsy findings, in a series of 1064 intrauterine deaths in the second and third trimesters, and subdivided according to gestational age at death

Overall cause of death	All (*n* = 1064)	Early IUFD (*n* = 246)	Late IUFD (*n* = 179)	Stillbirth (*n* = 639)
Abruption	38 (4)	3 (1)	5 (3)	30 (5)
Ascending infection	176 (17)	58 (24)	59 (33)	59 (9)
Birth trauma	7 (1)	0 (0)	0 (0)	7 (1)
Congenital abnormality	50 (5)	9 (4)	5 (3)	36 (6)
Fetomaternal hemorrhage	6 (1)	0 (0)	0 (0)	6 (1)
Infection	13 (1)	0 (0)	1 (1)	12 (2)
Known cord accident	4 (<1)	1 (<1)	1 (1)	2 (<1)
Known IUGR	17 (2)	4 (2)	5 (3)	8 (1)
Placenta	60 (6)	1 (<1)	4 (2)	55 (9)
Pre-eclampsia	16 (2)	0 (0)	0 (0)	16 (3)
Preterm	4 (<1)	0 (0)	3 (2)	1 (<1)
Twin complication	21 (2)	8 (3)	4 (2)	9 (1)
Unexplained (all)	652 (61)	162 (66)	92 (51)	398 (62)
Unexplained, lesion	125 (19)	19 (8)	10 (6)	96 (15)
Unexplained, obese	83 (13)	27 (11)	9 (5)	47 (7)
Unexplained, post-term	29 (4)	0 (0)	0 (0)	29 (5)
Unexplained, previous fetal loss	100 (15)	43 (17)	16 (9)	41 (6)
Unexplained, unexplained	292 (45)	69 (28)	54 (31)	169 (26)
Unexplained, diabetes	24 (4)	4 (2)	3 (1)	16 (3)

Data are given as *n* (%). Early intrauterine fetal death (IUFD) was defined as intrauterine death < 20 weeks, late IUFD was death at 20–23 weeks and stillbirth was death ≥ 24 weeks. IUGR, intrauterine growth restriction.

Table 2 Cause of intrauterine death in 752 cases according to maternal ethnicity

	Maternal ethnicity				
Cause of death	Caucasian	Mixed/ oriental	Asian	Black	Total
Abruption	15 (3)	0 (0)	5 (9)	7 (3)	27 (4)
Ascending infection	48 (10)	3 (17)	12 (21)	69 (33)	132 (18)
Birth trauma	2 (<1)	0 (0)	1 (2)	0 (0)	3 (<1)
Congenital abnormalities	18 (4)	0 (0)	2 (3)	7 (3)	27 (4)
Feto-maternal Haemorrhage	3 (1)	1 (6)	0 (0)	0 (0)	4 (1)
Infection	6 (1)	2 (11)	0 (0)	1 (<1)	9 (1)
Known cord accident	3 (1)	0 (0)	0 (0)	1 (<1)	4 (1)
Known IUGR	10 (2)	0 (0)	3 (5)	2 (1)	15 (2)
Placenta	39 (7)	0 (0)	3 (5)	7 (7)	49 (7)
Pre-eclampsia	5 (1)	0 (0)	0 (0)	5 (2)	10 (1)
Preterm	0 (0)	0 (0)	0 (0)	3 (1)	3 (<1)
Twin Complication	9 (2)	0 (0)	0 (0)	2 (1)	11 (1)
Unexplained (all)	311 (67)	12 (67)	32 (55)	103 (50)	458 (61)
Total	469 (62)	18 (2)	58 (8)	207 (28)	752

Data are given as *n* or *n* (%). There was no maternal ethnicity information in 312 cases, which have been excluded from the table.

Table 3 Cause of intrauterine death in 1039 cases according to maternal age

	Maternal age			
Cause of death	≤ 35 years	36–40 years	≥ 41 years	Total
Abruption	28 (4)	7 (4)	1 (2)	36 (3)
Ascending infection	130 (16)	36 (19)	8 (17)	174 (17)
Birth Trauma	6 (<1)	0 (0)	0 (0)	6 (<1)
Congenital abnormalities	39 (5)	6 (3)	4 (8)	49 (5)
Feto-maternal Hameorrhage	4 (<1)	1 (<1)	1 (2)	6 (<1)
Infection	11 (1)	1 (<1)	1 (2)	13 (1)
Known cord accident	4 (<1)	0 (0)	0 (0)	4 (<1)
Known IUGR	14 (2)	3 (2)	1 (2)	18 (2)
Placenta	45 (6)	9 (5)	6 (13)	60 (6)
Pre-eclampsia	14 (2)	2 (1)	0 (0)	16 (2)
Pre-term	4 (<1)	0 (0)	0 (0)	4 (<1)
Twin complications	16 (2)	4 (2)	1 (2)	21 (2)
Unexplained (all)	483 (60)	124 (64)	25 (52)	632 (61)
Total	798 (77)	193 (19)	48 (5)	1039

Data are given as *n* or *n* (%). There was no maternal age information in 25cases, which have been excluded from the table.

Table 4 Cause of intrauterine death in 466 cases according to maternal body mass index (BMI) category

	BMI category				
Cause of death	Underweight	Normal	Overweight	Obese	Total
Abruption	1 (5)	3 (2)	4 (2)	2 (1)	10 (2)
Ascending Infection	5 (23)	25 (18)	30 (19)	24 (16)	84 (18)
Birth Trauma	0 (0)	1 (<1)	3 (2)	0 (0)	4 (<1)
Congenital abnormalities	1 (5)	8 (6)	5 (3)	5 (3)	19 (4)
Feto-maternal Haemorrhage	0 (0)	0 (0)	1 (1)	0 (0)	1 (<1)
Infection	0 (0)	1 (<1)	2 (1)	6 (4)	9 (2)
Known cord accident	0 (0)	0 (0)	0 (0)	1 (1)	1 (<1)
Known IUGR	1 (5)	5 (4)	2 (1)	3 (2)	11 (2)
Placenta	0 (0)	10 (7)	8 (5)	6 (3)	24 (5)
Pre-eclampsia	0 (0)	4 (3)	2 (1)	2 (1)	8 (2)
Pre-term	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)
Twin Complication	0 (0)	1 (<1)	6 (4)	4 (3)	11 (2)
Unexplained (all)	13 (62)	78 (57)	99 (61)	93 (64)	283 (61)
Total	21 (5)	137 (29)	162 (35)	146 (31)	466

Data are given as *n* or *n* (%). There was no maternal BMI information in 598 cases, which have been excluded from the table. There was no association between specific causes of intrauterine death and maternal BMI, the majority of deaths being unexplained.

Table 5 Cause of intrauterine death in 894 cases according to fetal maceration

	Maceration				
Cause of death	None	Mild	Moderate	Severe	Total
Abruption	23 (7)	2 (2)	2 (3)	8 (2)	35 (4)
Ascending Infection	125 (39)	22 (18)	5 (8)	16 (4)	168 (19)
Birth Trauma	7 (2)	0 (0)	0 (0)	0 (0)	7 (1)
Congenital abnormalities	9 (3)	2 (2)	3 (5)	22 (6)	36 (4)
Feto-maternal Haemorrhage	1 (<1)	0 (0)	0 (0)	5 (1)	6 (1)
Infection	3 (<1)	2 (2)	1 (2)	4 (1)	10 (1)
Known cord accident	1 (<1)	3 (3)	0 (0)	0 (0)	4 (<1)
Known IUGR	5 (2)	3 (3)	1 (2)	5 (1)	14 (2)
Placenta	3 (1)	7 (6)	8 (14)	31 (8)	49 (5)
Pre-eclampsia	3 (<1)	4 (3)	1 (2)	2 (1)	10 (1)
Pre-term	4 (1)	0 (0)	0 (0)	0 (0)	4 (<1)
Twin Complication	12 (4)	1 (<1)	0 (0)	5 (1)	18 (2)
Unexplained (all)	128 (40)	73 (61)	38 (64)	294 (75)	533 (60)
Total	324 (36)	119 (13)	59 (7)	392 (44)	894

Data are given as *n* or *n* (%). There was no maceration information in 170 cases, which have been excluded from the table. A stepwise increase in the percentage of unexplained cases was seen with increasing maceration. This persisted even following removal of cases of ascending infection from the analysis.

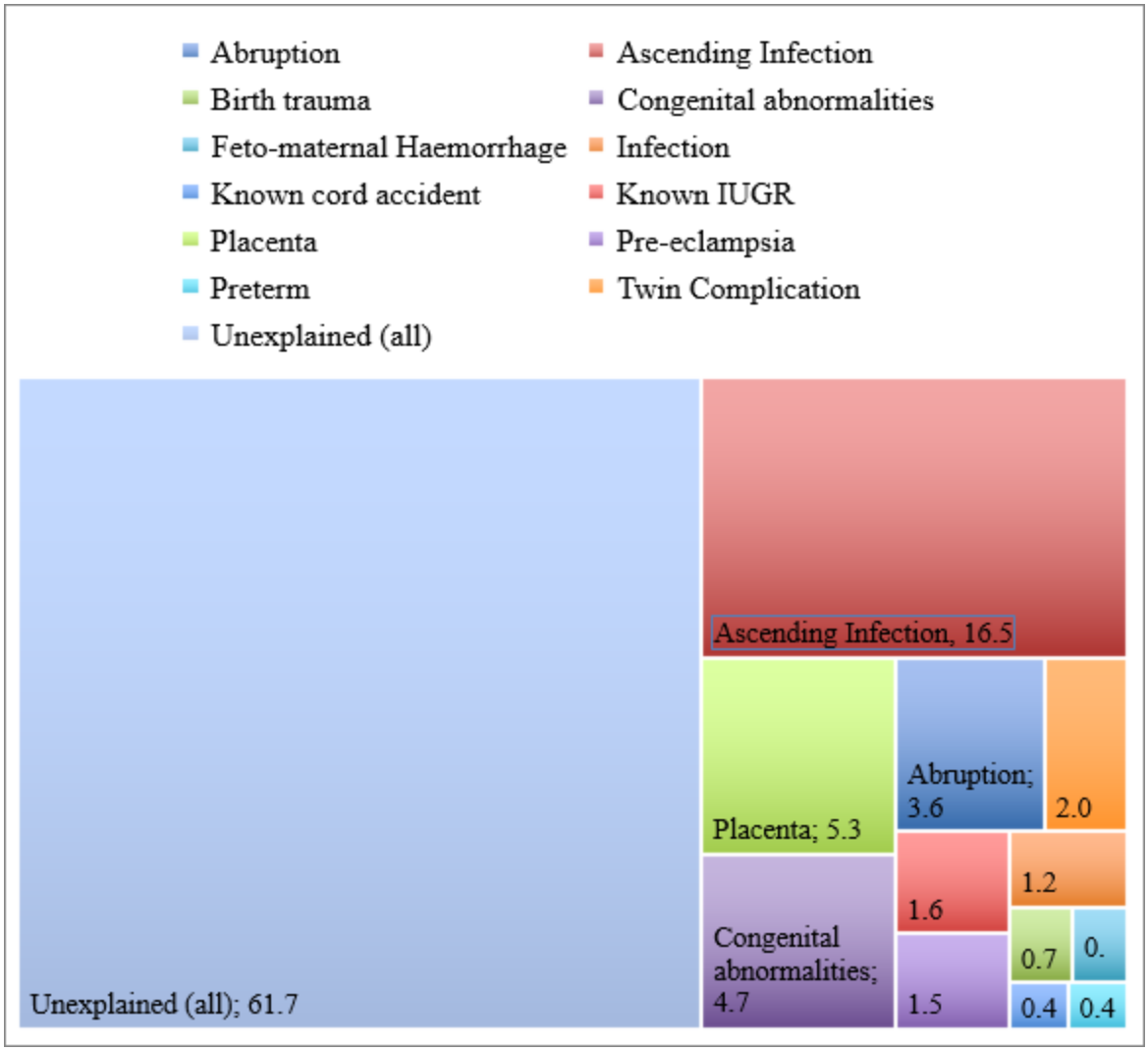

Figure S1 Overall cause of death, with percentage prevalence, defined objectively based on autopsy findings in a series of 1064 intrauterine deaths in the second and third trimesters.

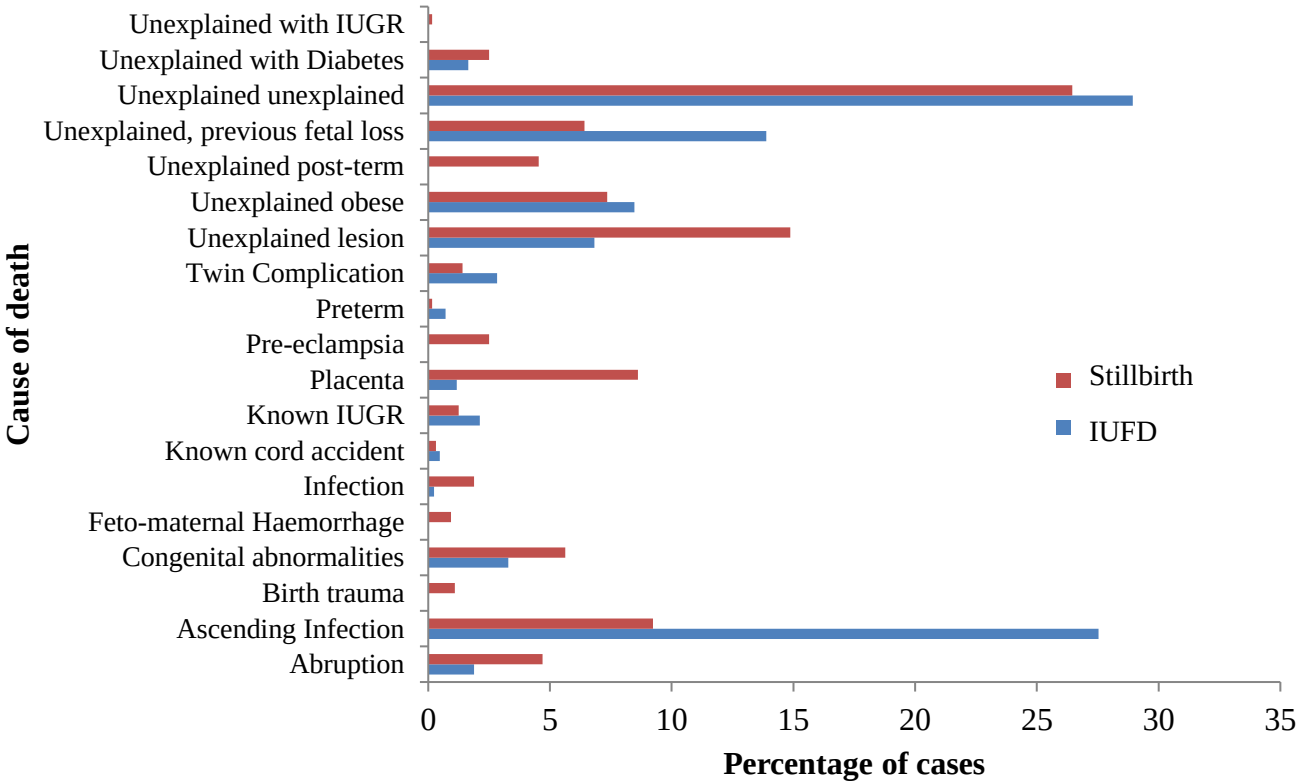

Figure S2 Simplified cause of death, based on autopsy findings, in 1064 cases of intrauterine death, according to gestational age at death.

Intrauterine fetal death (IUFD) was < 23 weeks and stillbirth was ≥ 24 weeks.

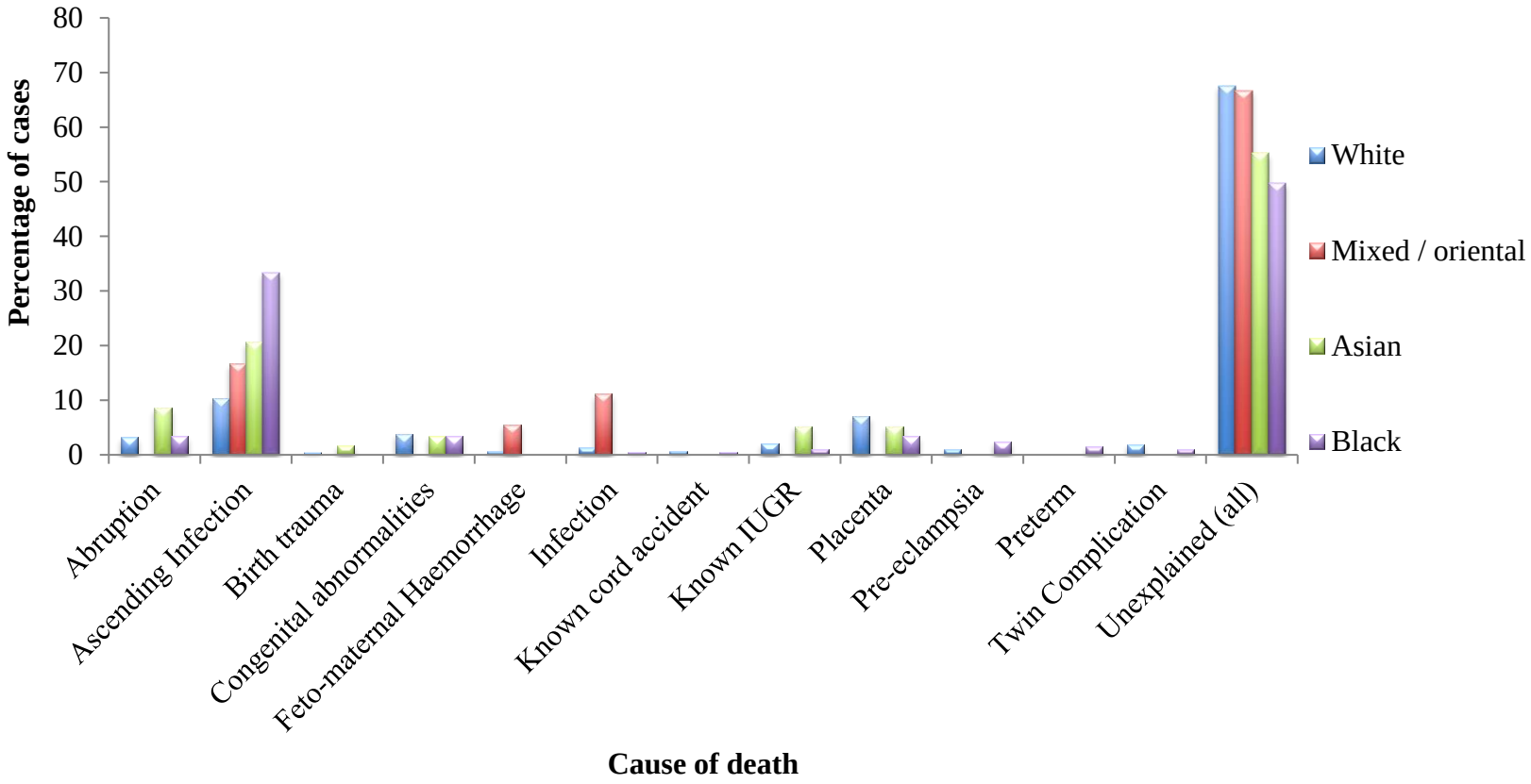

Figure S3 Cause of intrauterine death in 752 cases according to maternal ethnicity. Black and Asian mothers had a significantly greater proportion of deaths associated with ascending infection than did white mothers.

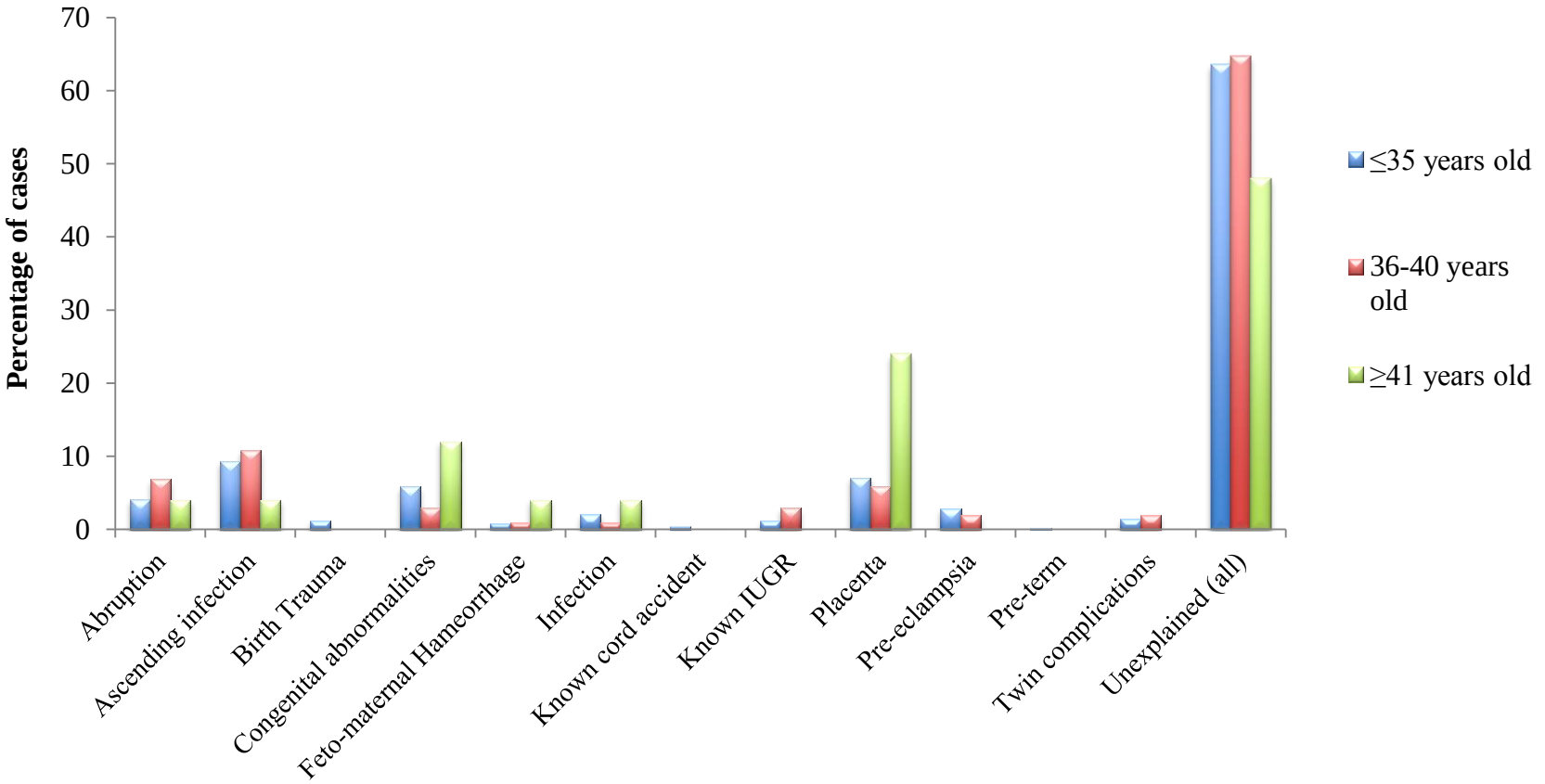

Figure S4 Cause of intrauterine death in 1039 cases according to maternal age. There were significantly more placenta-related causes of death in mothers over 40 years old.

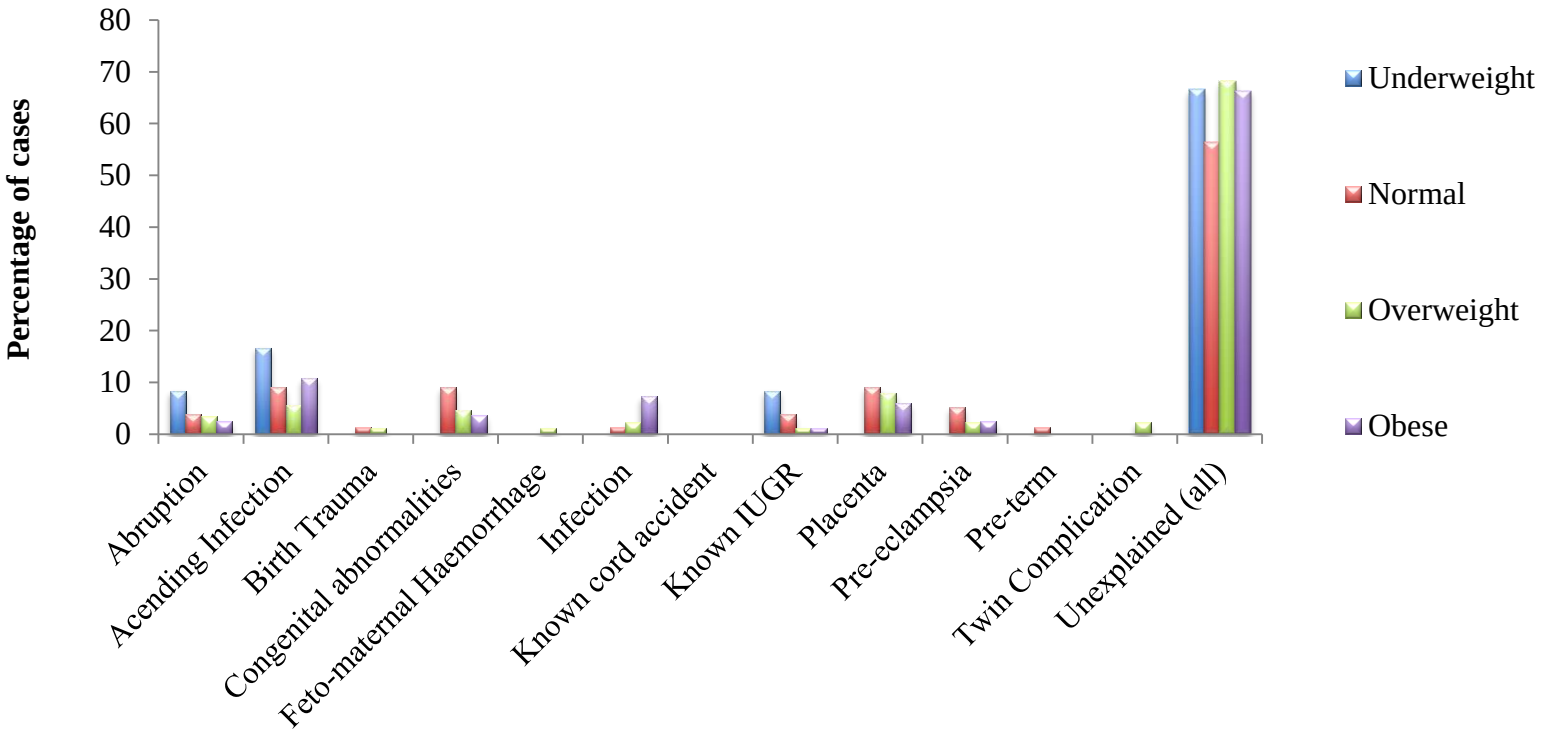
Percentage of cases
80
70
60
50
40
30
20
10
0
Underweight
Normal
Overweight
Obese
Abruption
Acending Infection
Birth Trauma
Congenital abnormalities
Feto-maternal Haemorrhage
Infection
Known cord accident
Known IUGR
Placenta
Pre-eclampsia
Pre-term
Twin Complication
Unexplained (all)

Figure S5 Cause of intrauterine death in 466 cases according to maternal body mass index (BMI) category. No association between specific causes of intrauterine death and maternal BMI was observed.

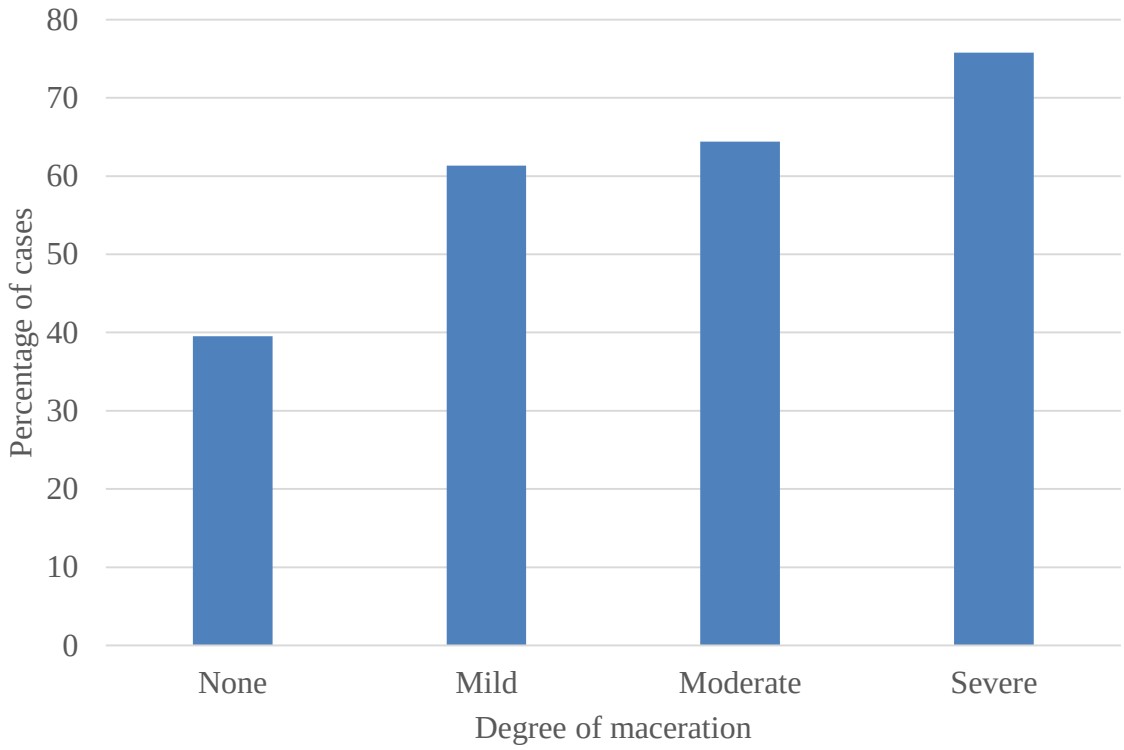

Figure S6 Percentage of unexplained intrauterine deaths (*n* = 533) according to degree of fetal maceration. A stepwise increase in unexplained deaths was seen with increasing maceration (which persisted even when deaths due to ascending infection were removed from the analysis).

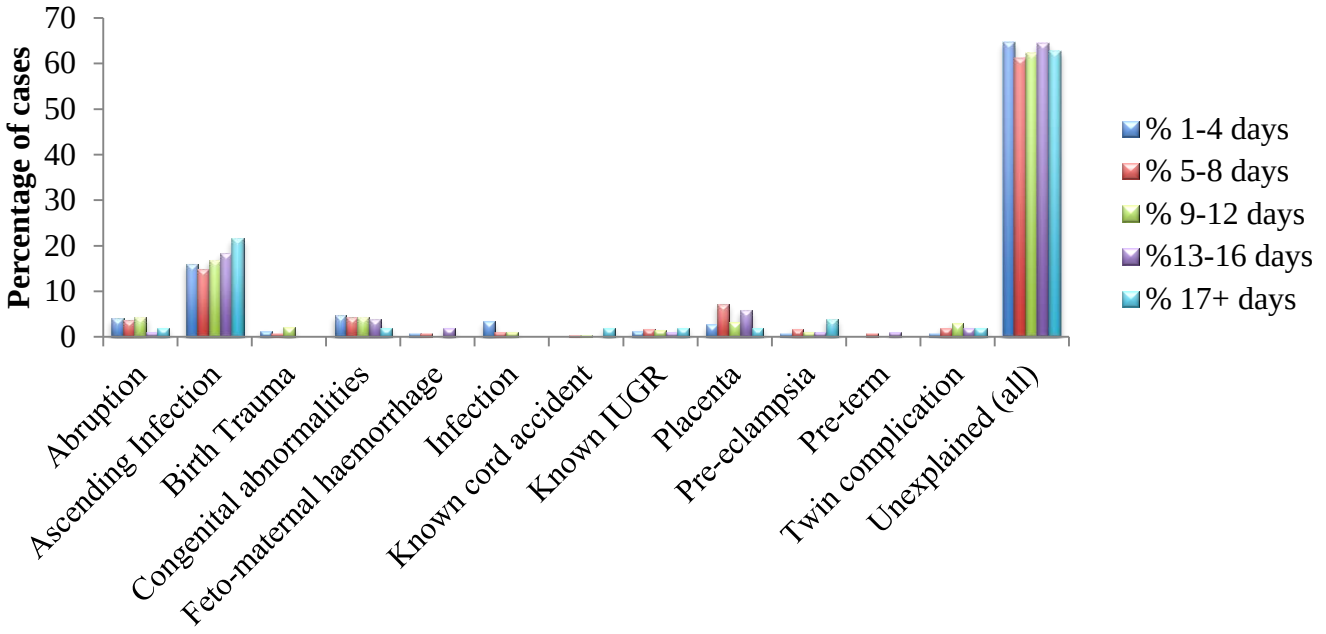

Figure S7 Cause of intrauterine death according to duration of postmortem interval (PMI) There was no significant effect of PMI on determination of overall cause of death.

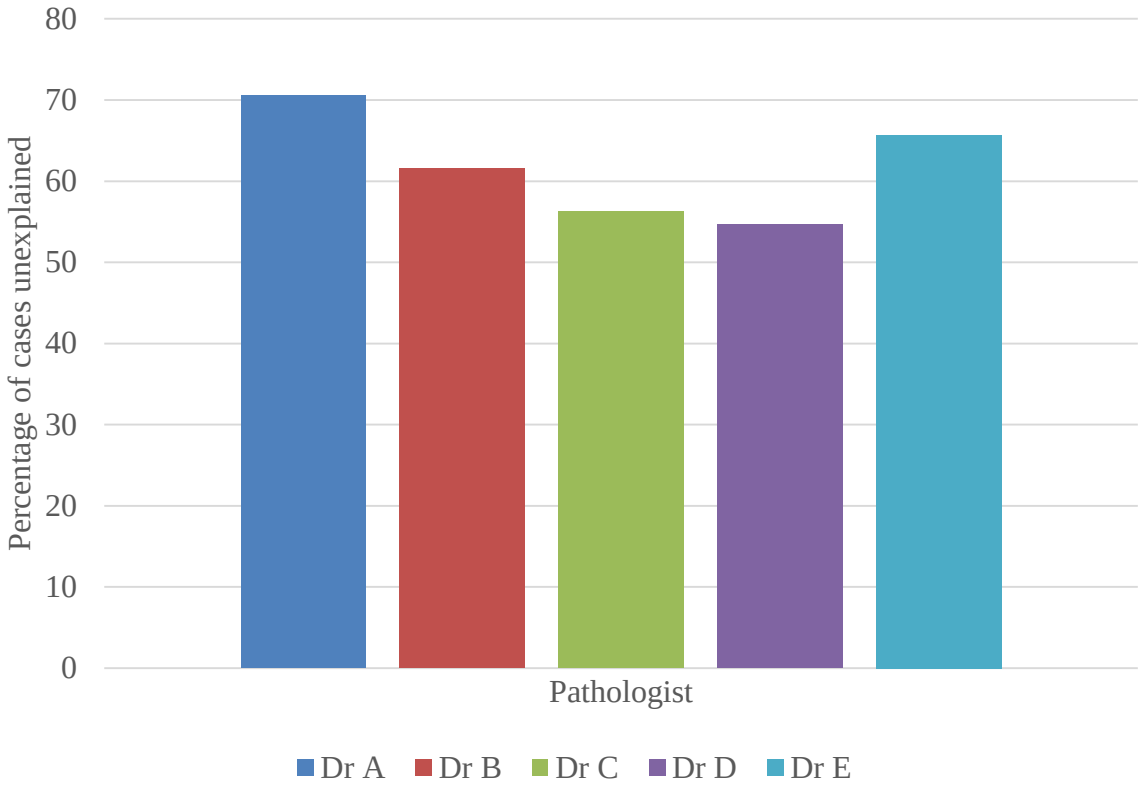

Figure S8 Percentage of 1064 intrauterine deaths that were unexplained by particular pathologists. When predefined criteria were used based on objective autopsy findings, there was no significant difference in rate of unexplained deaths between pathologists.

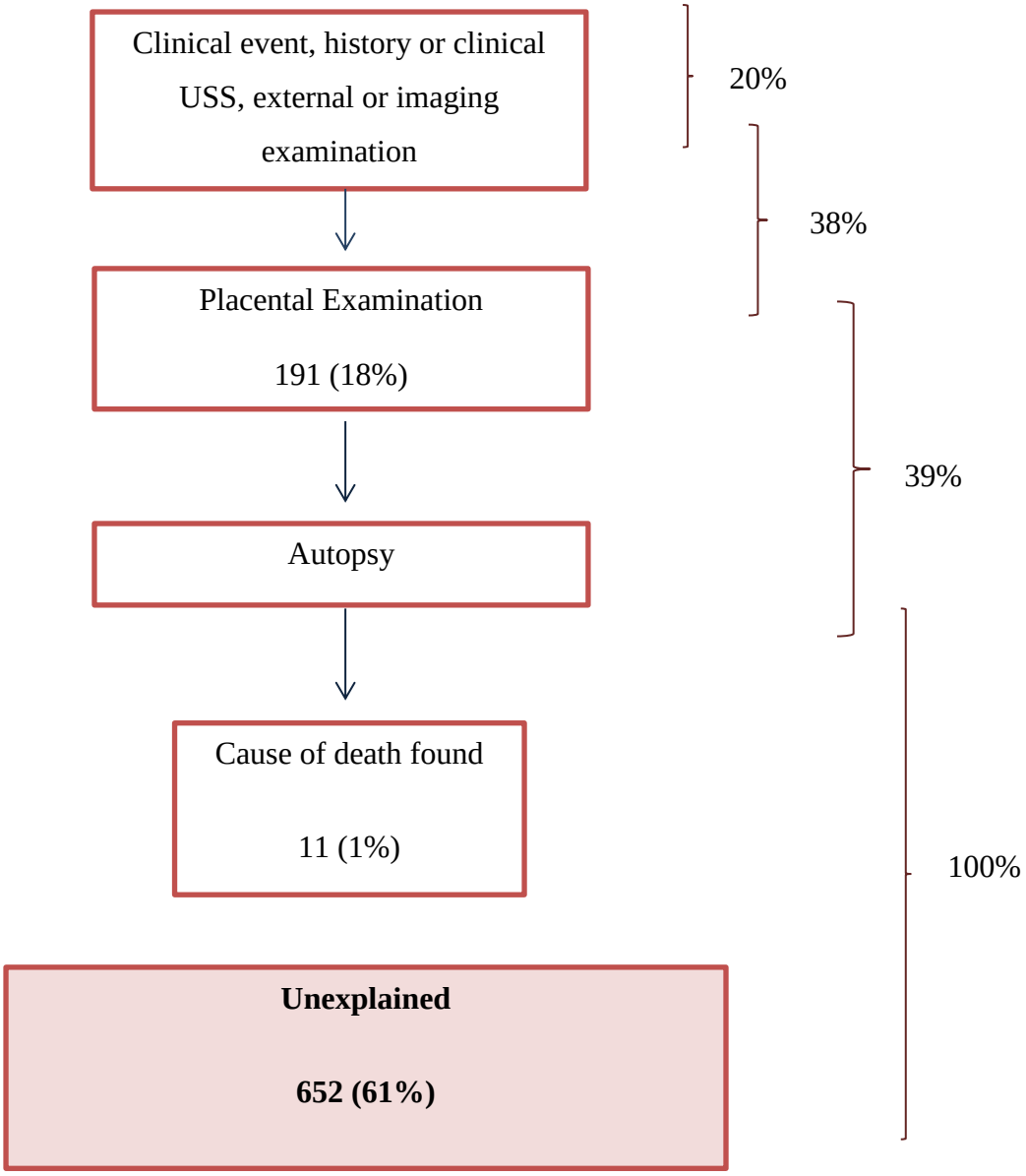

Figure S9 Proportion of cases that were allocated a cause of death using clinical history, antenatal ultrasound scan (USS) or postmortem imaging/external examination (20%), placental examination (18%) or autopsy (1%) and those remaining unexplained (61%).