

Aetiological Classification of Stillbirths: A Case Control Study

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About the Author



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Abstract Antepartum stillbirths are a major contributor to perinatal mortality. This study was undertaken to assess the role of the ReCoDe (relevant condition at birth) classification system in evaluation of stillbirths in a tertiary teaching hospital in Central Gujarat.

Aim To determine etiology of stillbirths using the ReCoDe classification system.

Materials and Methods This was a prospective case control study over a period of 1 year from September 1st,

2012 to August 31st, 2013. Sample size was calculated as 243 cases and 486 controls. Two controls (live births) per case were matched for gestational age and birth weight. Odd's ratios with 95 % confidence intervals were calculated using multivariate logistic regression.

Results Maternal age and parity that appeared to be highly significant factors on univariate analysis were not found to be independent risk factors with multivariate logistic regression. Gestational age and birth weight were not statistically significant risk factors. Other risk factors like previous stillbirth (26.13; 95 % CI 3.23–211.29), antepartum hemorrhage (11.63; 95 % CI 3.83–35.30), and hypertensive disorders (2.09; 95 % CI 1.20–3.63) were found to be highly significant independent risk factors. Major congenital anomaly ($P < 0.001$), birth asphyxia ($P = 0.0037$), cord accidents ($P = 0.0037$), and rupture uterus ($P = 0.001$) were also highly significant.

Conclusion The stillbirth rate was 87.83 per 1000 live births. The ReCoDe primary classification system enabled

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74.1 % of the cases to be assigned a relevant condition, leaving only 25.9 % as unexplained. The single largest condition associated was fetal growth restriction (25.9 %).

Keywords Birth weight · Gestational age · Intrauterine growth restriction · ReCoDe · Stillbirths

Background

The definition of stillbirth differs in the developed and developing countries, depending upon the potential of the neonatal intensive care setups to salvage low birth weight and premature babies. The ICD 10 defines fetal death as death prior to complete expulsion or extraction from its mother irrespective of the period of gestation (POG) [1]. For international comparison, the WHO defines stillbirth as a baby born with no signs of life at or after 28 weeks gestation or if weight is more than 1000 g if POG is not available [2]. The Perinatal Mortality Surveillance Report (CEMACH) has defined stillbirth as a baby delivered with no signs of life known to have died after 24 completed weeks of pregnancy [3].

Antepartum stillbirths are a major contributor to perinatal mortality. A large proportion of these deaths have no apparent cause. In literature, the proportion of stillbirths without a known cause of death varies from 7 to 82 %. The lowest rates of stillbirths have been reported from Finland and Singapore (2.0 per 1000 births) and from Norway and Denmark (2.2 per 1000 births). Most of the stillbirths occur in the developing nations, with ten countries (Pakistan, Nigeria, China, Democratic Republic of the Congo, Ethiopia, Bangladesh, Indonesia, Tanzania, Afghanistan, and India) accounting for over two-thirds of all cases [4].

The new ReCoDe [5] classification system was derived after conducting a population-based cohort study in the West Midlands Region (Perinatal Institute) over a period of 7 years from 1997 to 2003. This system reduces the predominance of stillbirths currently classified as unexplained. By the ReCoDe classification system, the most common cause was fetal growth restriction (43 %) and only 15.2 % of stillbirths remained unexplained. Moreover, ReCoDe can identify relevant conditions at the time of death in about 85 % of the cases. This study was conducted to establish an etiological classification of stillbirths according to the ReCoDe system.

Methods and Materials

This was a prospective case control study over a period of 1 year from September 1st, 2012 to August 31st, 2013 conducted in the department of Obstetrics and Gynecology, Medical College Baroda, Gujarat.

A pilot study was performed for 1 month prior to the study period to establish common risk factors in our

population, which would enable the sample size estimation. With the help of an expert from the Department of Preventive and Social Medicine, Medical College, Vadodara, a power of 90 % and an alpha error of 5 was agreed upon and, sample size was calculated as 243 cases with 486 controls in the case to control ratio of 1:2.

All antepartum stillbirths with gestational age >28 weeks were considered eligible for inclusion in the study. Stillbirths in multiple gestations and singletons less than 1000 g (where exact gestational age is not known) were excluded from the study. Gestation age was confirmed by known LMP or first trimester antenatal ultrasound; where the weeks of gestation were not known, the gestational age was rounded off to the nearest week.

Two controls (live births) per case were matched for gestational age and birth weight after taking a written informed consent from both cases and controls. Matching for birth weight was carried out because a number of known risk factors for stillbirths are thought to be mediated through low birth weight. It is impossible to match birth-weights exactly; therefore controls were matched within 100 g of weight.

Intrauterine growth restriction was predicted on the basis of Ponderal index (PI) which is calculated as [birth weight in grams/(crown heel length in cms) [3]] \times 100. Those fetuses that had a PI >2 were said to have Symmetrical IUGR whereas those who had a PI <2 were said to have Asymmetrical IUGR.

Data Collection and Statistical Analysis

Data relating to socio-demographic information, past obstetric history, associated medical conditions, index pregnancy characteristics were collected for each case. Stillbirths were classified according to the ReCoDe classification system [5] (Table 1). This system seeks to establish a probable cause for stillbirths. Fetal growth restriction (A7) was defined according to the fetal anthropometric measurements (height, weight, and head circumference and ponderal index). Small for gestational age was defined as a newborn birth weight below the 10th centile for gestational age and gender. The investigators were not blinded for outcomes during the data extraction process.

All data were entered into an excel sheet. Odd's ratios with 95 % confidence intervals were calculated using multivariate logistic regression using Epi-Info version 3.5.1. Statistical significance was set at $P < 0.05$.

Results

There were total 506 stillbirths over this study period and 5761 total births. Of these, 243 stillbirths that fulfilled the inclusion criteria were recruited for the study. Inclusions

Table 1 ReCoDe classification system of etiological classification of stillbirths (relevant condition at death)

Group A: fetus
1. Congenital anomaly
2. Infection
2.1 Acute
2.2 Chronic
3. Non immune hydrops
4. Isoimmunisation
5. Feto maternal hemorrhage
6. Twin–twin transfusion
7. Fetal growth restriction
Group B: umbilical cord
1. Prolapse
2. Constricting loop or knot
3. Velamentous insertion
4. Other
Group C: placenta
1. Abruptio
2. Praevia
3. Vasa praevia
4. Other placental insufficiency
5. Other
Group D: amniotic fluid abnormalities
1. Chorioamnionitis
2. Polyhydramnios
3. Oligohydramnios
Group E: uterus
1. Rupture
2. Uterine anomalies
3. Other
Group F: mother
1. Diabetes
2. Thyroid disease
3. Essential hypertension
4. Hypertensive diseases in pregnancy
5. Lupus or antiphospholipid syndrome
6. cholestasis
7. Drug misuse
8. Other
Group G: intrapartum
1. Asphyxia
2. Birth trauma
Group H: trauma
1. External
2. Iatrogenic
Group I: unclassified
1. No relevant condition identified
2. No information available

were stopped when the numbers needed according to the sample size calculation were met. The stillbirth rate was 87.83 per 1000 live births.

The distribution of gender among cases and controls was 58.02 % ($n = 141$) males among cases and 59.67 % ($n = 296$) males among controls whereas 41.98 % ($n = 102$) females among cases and 40.33 % ($n = 200$) females among controls. Thus, gender was not a statistically significant factor for causing stillbirths ($P = 0.7265$).

Table 2 shows that there was no difference in the mean \pm SD values for birth weight and gestational age between the two groups; however, the mean \pm SD values for maternal age and parity were highly significant on univariate analysis.

Thirteen women among the cases had a previous history of stillbirth whereas only one woman in the control group had a recurrence of stillbirth. The odd's ratio (OR) for a recurrent stillbirth was 27.97 (95 % CI 3.638; 215.168).

Factors like maternal age ($P = 0.0000$) and parity ($P = 0.0067$) that appeared to be highly significant on univariate analysis (Fig. 1; Table 3) were not found to be independent risk factors on multivariate analysis.

Various other factors like antepartum hemorrhage (OR 11.63; 95 % CI 3.83–35.30) and hypertensive disorders (OR 2.09; 95 % CI 1.20–3.63) were found to be highly significant independent risk factors on multivariate analysis. Major congenital anomaly ($P < 0.001$), birth asphyxia ($P = 0.0037$), cord accidents ($P = 0.0037$), and rupture uterus ($P = 0.001$) were also highly significant.

Table 4 shows that 25.9 % cases had growth restriction and in an equal percentage of cases there was no cause identified. Placental histopathology was performed in only 30 cases on the basis of relevant history like antenatally diagnosed pre-eclampsia, previous stillbirth, and abnormal placenta on gross examination. Placental histopathology could reveal chorioangioma in one of the cases. Out of 243 stillbirths, 88.5 % ($n = 215$) were fresh stillbirths whereas only 11.5 % ($n = 28$) were macerated stillbirths.

Discussion

This study has outlined the causes of stillbirths in our study population based on the ReCoDe [5] system. The ReCoDe classification system was selected over the other existing systems because in the ReCoDe system the proportion of cases defined as unexplained stillbirths is only 15 %. Also the ReCoDe classification system is among the four classification systems (CODAC, PSANZ-PDC, ReCoDe, and Tulip) which performed well on the Infokeep score [6].

Table 2 Mean values for birthweight, gestational age, maternal age, and parity

	Cases	Controls	Standard error of difference of mean		
			SD	95 % CI	P value
Birth weight in grams (mean \pm SD)	1806.45 \pm 596.25	1755.17 \pm 597.58	46.758	−143.07 to 40.51	0.2731
Gestational age in weeks (mean \pm SD)	33.55 \pm 3.91	33.41 \pm 3.92	0.307	−0.742 to 0.462	0.6482
Maternal age in years (mean \pm SD)	26.36 \pm 5.06	23.43 \pm 3.43	0.316	−3.551 to −2.309	<0.0001
Parity (mean \pm SD)	2.17 \pm 1.26	1.61 \pm 0.88	0.0799	−0.717 to −0.403	<0.0001

Table 3 Odd's ratios for various risk factors

Risk factor	Odd's ratio	95 %	C.I.	P value
Antepartum hemorrhage	11.6318	3.8324	35.3040	0.0000
Hypertension	2.0968	1.2083	3.6388	0.0085
IUGR	1.1356	0.7634	1.6892	0.5304
Maternal age	0.8655	0.8288	0.9039	0.0000
Oligohydramnios	2.9396	0.9842	8.7800	0.0534
P/H/O SB	26.1358	3.2328	211.2945	0.0022
Parity	0.7908	0.6673	0.9371	0.0067
Postdatism	2.4747	0.4318	14.1816	0.3090

The ReCoDe primary classification system enabled 74.1 % of the cases to be assigned a relevant condition, leaving only 25.9 % as unexplained. The single largest condition associated was fetal growth restriction (25.9 %). Ponderal index was used to identify infants with in utero growth restriction, which is not the ideal method to estimate growth restriction. The ratio of IUGR among cases and controls was found to be nearly 1:2 which explains why it was not a significant risk factor in causing stillbirths. Hence, intrauterine growth restriction was not a significant risk factor at $P = 0.5457$.

Gardosi et al. [5] found that of the 66.2 % stillbirths who remained as unclassified according to the Wigglesworth system of classification, most stillbirths were growth restricted. So the largest category of stillbirths was A7 (IUGR) i.e., 47 %. Only 15.2 % cases remained unclassified after applying ReCoDe system (relevant condition at death). Hence, this system enabled 85 % of the cases to be assigned a relevant condition, leaving only 15 % as unexplained. ReCoDe identified 57.7 % of the Wigglesworth unexplained stillbirths as growth restricted.

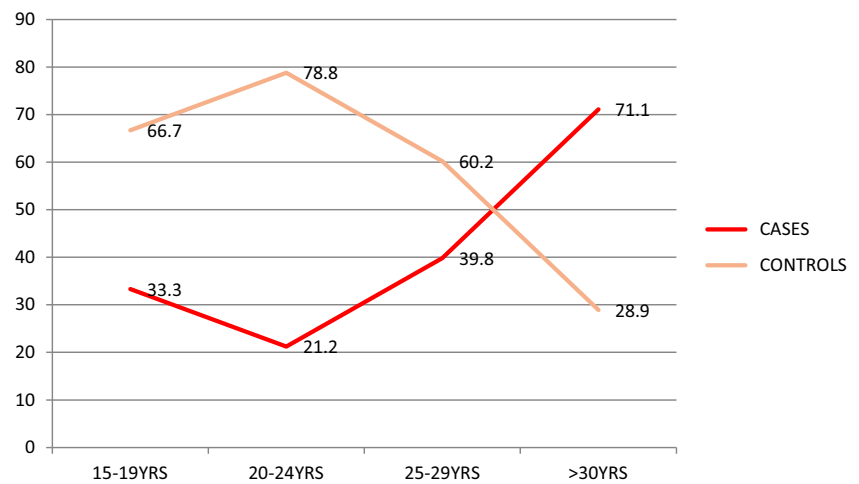
The present study did not find gender a significant risk factor. Smith et al. [7] found that the relative risk for male stillbirths was 1.19 which varied according to birth weight quintile. The main finding was that the increased risk of stillbirth associated with male gender progressively diminishes with increasing birth weight.

In our study, the cases and controls were matched for birthweight and gestational age. Robalo et al. [8] examined the etiological factors contributing to late fetal death over a 10-year period through a retrospective cohort study. The

cause of death was classified according to the ReCoDe system similar to the present study. Unexplained stillbirths contributed to 24.5 % cases consistent with previous studies. The percentage contribution of other factors like fetal pathology (28.4 %), placental factors (26.9 %), maternal conditions (21.2 %), amniotic fluid disorders (10.6 %), and umbilical cord events (9.6 %) was drawn. However, the independent behavior of all these factors in causing stillbirths was not commented upon.

Huang et al. [9] found that greater maternal age was significantly associated with increased risk of stillbirth; relative risks varied from 1.20 to 4.83 for older versus younger women. Apart from the present study, few more studies [10] demonstrated a statistically significant increase in stillbirths with increased maternal age, which was identified as an independent risk factor on multivariate analysis whereas others [11] conclude that an increased risk for stillbirth is associated with both extremes of maternal age.

Onwude et al. [12] performed a matched case control study in which 75 women who delivered stillbirths were matched with 75 controls and concluded that a woman who has had an unexplained stillbirth at term has no greater risk of recurrence than a matched control. In the present study, however, there were 13 cases with history of previous stillbirth as compared to only one in the control group, giving an Odd's Ratio 27.97 (95 % CI, 3.64;215.15). Bhattacharya et al. [13] showed that after adjusting for confounding factors, the odd's ratio of recurrence of stillbirths in a second pregnancy was found to be 1.94 (99 % CI 1.29–2.92).

Fig. 1 Distribution of stillbirths according to maternal age**Table 4** Frequency and percentage distribution according to ReCoDe system

Condition	Frequency (n)	Percentage (%)
Group A: fetus		
Congenital anomaly	6	2.46
Fetal growth restriction	63	25.9
Group B: umbilical cord		
Prolapse	5	2.05
Group C: placental		
Abruption	19	7.81
Praevia	6	2.46
Chorioangioma	1	0.41
Group D: amniotic fluid		
Polyhydramnios	0	0
Oligohydramnios	7	2.88
Group E: uterus		
Rupture	6	2.46
Uterine anomaly	1	0.41
Group F: mother		
Hypertensive disorders in pregnancy	30	12.34
Cholestasis	4	1.64
Group G: intrapartum		
Asphyxia	5	2.05
Group H: trauma		
External	1	0.41
Group I: unclassified		
Unidentified	63	25.9

Strengths and Limitations of the Study

The confounding effect of low birth weight in causing stillbirth was nullified by matching the cases and controls for birth weight. The prospective nature of data collection precludes recall bias.

Ponderal index was used to estimate the fetal growth restriction in contrast to GROW version 4.6 that was used by Gardosi et al. [5], which is an ideal method of assessment of growth restriction. Also, fetal autopsy and radiological assessment for cause of death was performed only in a few cases.

Implications for Clinical Practice

More than 90 % of women among cases presented with absent fetal heart sounds implying that antepartum stillbirths are preventable with the use of adequate and cautious antenatal surveillance of risk factors. Most of the fetuses had reached a gestational age at which they could have been salvaged, had timely intervention been available.

Conclusion

The new ReCoDe primary classification system facilitated assigning the probable cause of death in 74.1 % cases in the study population. Intrauterine growth restriction, which is a preventable condition, constituted the maximum number of cases. The need for a complete work up regarding cause of death is crucial for counseling the parents for their future pregnancies.

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Compliance with Ethical Requirements and Conflict of interests All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 as revised in 2008 (5). Informed consent was obtained from all patients (cases and controls) being included in the study. Sonal Kumbhare and Nandita Maitra declare that they have no conflict of interest.

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