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Do Anomalous Stillbirths Have Risk To Be Delivered Preterm? A Cross-Sectional Study Conducted in Kandy, Sri Lanka

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Abstract

Stillbirths is one of major health issues in Sri Lankan context. This study aimed to explore the distribution of externally identifiable congenital anomalies according to their sex and the period of gestation and to estimate risk of stillbirth with or without congenital anomalies to be born pre-term or term. Sample size was 246. Due to extreme prematurity and maceration, 05 fetuses were excluded. Of 241 stillbirths, 36 (14.9%) had congenital anomalies and majority were females (n=23, 9.5%). The mean period of gestation was 31 weeks (SD=5.3). 12.5% with congenital anomalies were pre-term. 95% confidence interval (0.261-1.170) of risk estimate revealed that there is no statistically significant association between fetal sex and having congenital anomalies. Risk to be preterm stillbirth for the fetuses with congenital anomalies was 2.447 times (OR = 2.447) greater than the non-anomulous. Females were at high risk to acquire congenital anomalies. Congenital anomalies caused preterm stillbirths.

Introduction

Stillbirth is a traumatic experience for mothers, families, and society. World Health Organization (WHO) defines stillbirth as the delivery of a fetus with no sign of life at or after 28 weeks of gestation or weighing 500g or more[1]. This definition was used as a standard definition for a worldwide survey on stillbirths and as the cut-off period of gestation (POG) in studies in India and Nepal[2,3,4]. However, it is obvious from various research, that different cut-off gestational weeks are used by various countries to describe stillbirths. Numerous studies carried out in the United States (US) had used 20 gestational weeks as the cut-off POG to select stillbirths while the United Kingdom chose 24 weeks[5,6,7,8,9]. The Lancet stillbirth series selected 22 weeks as the minimum POG for stillbirth except for the comparison with other international studies[10]. In the year 2015, the Ministry of Health, Sri Lanka released a circular letter on registration of Stillbirths defining 28 weeks of gestation[11]. According to the guidelines of national feto-infant mortality surveillance mechanism, introduced by the Ministry of Health, Sri Lanka instead of “stillbirths”, use of an umbrella term “fetal deaths” is advised.

The fetal deaths occurred at 22 weeks or after are included in that surveillance[12,13]. That particular suggestion encompasses a wider scope. Senanayake (2011), reported stillbirths are registered in Sri Lanka after 22 weeks[14]. Hence, the minimum gestation we used in this study was 22 weeks.

The global stillbirth statistics show that stillbirths are common in low- and middle-income countries[2]. In 2015, South-Asia was estimated as one of the regions with a high stillbirth rate (25.5 stillbirths per 1000 live births) that accountable for 967 000 stillbirths. Stillbirth rate for Sri Lanka in 2016 was 6.0 per 1000 live births and the total number of 1823 stillbirths was reported[15].

Stillbirth studies from many countries exhibited that some of the stillborn fetuses were affected by congenital malformations, deformations as well as chromosomal abnormalities. Data of Europe suggest that chromosomal anomalies have contributed to 28% of stillbirths aged from 20 gestational weeks[16]. Although there was no record found about that fact in the Sri Lankan setting, WHO Health Statistics in

2010 reported that 30% of under 5 years old children's mortality was due to congenital anomalies in Sri Lanka[17].

A number of congenital anomalies have been detected in stillborn fetuses. An Indian study reported that the highest number of birth defects among stillbirths belonged to the central nervous system (CNS) followed by the musculoskeletal system[18].

The frequency of stillbirths with congenital anomalies differs compared to fetal sex. Worldwide studies revealed males affected stillbirths higher than females while some showed females highly affected than males. An Indian study found the number of male stillborn babies presented with visible structural congenital malformations were greater than of females[19]. On the contrary, Michigan, US, statistics reported a slight increase in female stillbirths with congenital anomalies than males[20]. Regarding gestational age, the risk of stillbirth in anomalous fetuses was similar before 32 weeks gestation and after 32 weeks or more[21].

The global attention regarding researching on stillbirths and stillbirth associated risk factors is poor[2]. Similarly, the literature on stillbirth in Sri Lanka is hardly found. Some congenital malformations and chromosomal abnormalities lead to lethal effects on the live fetus in utero. Hence, it is vital to explore the presence of congenital anomalies among stillbirth fetuses. Identifying the types of congenital anomalies among stillbirths facilitates the health care personnel to recognize preventable circumstances before stillbirths occur. Moreover, this study would support the health system in Sri Lanka to bring stillbirth research forward.

Materials And Methods

This descriptive, cross-sectional study was implemented prospectively, where the data was collected from April 2017 to May 2018. Mainly, the four major hospitals of Kandy district were included. Teaching Hospitals, Kandy; Peradeniya; Gampola and General Hospital, Nawalapitiya were the major resources of data collection. In the Sri Lankan context, each year the rate of stillbirths has been reduced. However, the stillbirth rate of Kandy district showed a downward trend with fluctuations which increased in 2017 (Medical Statistics Unit, 2017)[15,22]. This instability motivated the researchers to select the Kandy district for the study.

The minimum POG used to select stillbirths was 22 weeks. The sample size was 246 and calculated according to the tables of minimum sample size for health studies, estimating the population proportion with specified absolute precision where confidence interval (CI) was 95%, absolute precision (d) was 0.05 and 0.2 of the anticipated population (P)[20]. All consecutive cases of stillbirths were included in the study from the beginning until the required sample size was obtained.

The study was approved by the Ethics Review Committee, Faculty of Medicine, University of Peradeniya. The permission was gained from the Directors, medical superintendents of hospitals, consultants

obstetricians and gynecologists, consultants pediatricians, nursing sisters, and in-charge nurses and staff members of the antenatal wards, postnatal wards, labor rooms, and operation theatres. Written, informed consent was taken from the mothers who participated in the study to examine the stillborn fetuses.

POG at the death of the fetus was obtained from the bed head tickets where the ward doctor had determined it using ultrasonography (USG) for mothers who were admitted to the hospital before delivery of the stillborn baby. For those, who were not diagnosed using USG, POG at death was calculated after the delivery[23]. The degree of maceration was determined by observing the stillborn fetus after the delivery. Intrauterine duration of retention of the fetus, according to the degree of maceration was deducted from the POG at the delivery of the stillborn fetus to estimate the approximate time of death.

Stillborn baby's body was examined by the main author to identify externally visible structural congenital malformations, deformations, and chromosomal abnormalities and to determine the degree of maceration. Within six hours soon after the delivery, the examination of the stillborn fetus was done. To enhance the accuracy of the anomalies identified, confirmation of the diagnosis was obtained from the consultant pediatricians of relevant hospitals. Subsequently, those congenital anomalies were classified according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD 10) for congenital malformations, deformations, and chromosomal abnormalities20[20].

The distribution of the stillbirths with anomalies was grouped according to the POG. The categories were "*extremely preterm*" (< 28 weeks); "*very preterm*" (28-<32 weeks); "*moderate to late preterm*" (32-<37 weeks); and "*term*" (≥ 37 weeks). The motive behind this categorization is to figure out the category where we need interventions to prevent stillbirths with the current health care system available in the country. Moreover, mean, standard deviation (SD), and 95% Confidence Interval (CI) of POG, were calculated for the stillbirths with congenital and chromosomal abnormalities and according to the sex of the fetus separately. Odds ratio (OR) was calculated to ascertain significance between the presence of congenital anomalies (present or absent) and sex of the fetus (male and female) and the POG of less and equal or greater than 37 weeks (< 37 and ≥ 37). When the distribution of fetal sex was analyzed according to the POG and displayed in the box-plot, gestational age determined by the weeks was converted to days.

All the collected data were entered into the SPSS version 19 datasheet and analyzed using descriptive statistics and crosstab.

Results

Among 246 stillborn babies, five cases were excluded as the body structures were not identifiable due to extreme prematurity and maceration. Therefore, for data analyzing purposes 241 cases were included.

The number of stillbirths with obvious structural congenital anomalies either malformations, deformations, or chromosomal abnormalities were detected among 36 (14.9%) fetuses out of 241 of the whole stillbirth sample. Of them, 34 (14.1%) fetuses were recognized with observable structural

congenital malformations and deformations while chromosomal abnormalities were found in 2 (0.8%) stillbirths. Female, male and unidentified fetal sex stillbirths frequencies were 23 (9.5%), 12 (5.0%) and 1 (0.4%) respectively. The mean POG of all stillbirths with congenital malformations and chromosomal abnormalities was 217 days (31 weeks) and SD ± 36.975. For stillbirths that did not show congenital anomalies, mean POG was 228.19 and SD ± 39.156.

One sample t test was done to see whether there is a significance difference between the mean POGs of stillbirths with and without congenital anomalies. Mean difference was − 10.246 and Significance (2-tailed) was 0.105. The 95% CI of the difference ranged between − 22.76 and 2.26. Thus the values revealed that there is no statistically significance between those two means of POGs.

Further, box and whisker plot illustrated the comparison between the distribution of POGs among male and female stillbirths with congenital anomalies.

According to the Fig. 1, POG was distributed within a vast difference of days among female babies with congenital anomalies than male stillborn infants, and the mean POG of them was higher than of males and the whole stillborn babies with congenital anomalies. The mean POG for male stillbirths with congenital anomalies was 213.42 (± 36.736) days and for females it was 223.09 (± 35.715).

The presence of congenital anomalies according to the fetal sex was calculated. The results are presented in the table I.

Table 1
Presence of congenital anomalies according to the fetal sex

Sex of the stillborn baby	Congenital anomalies		Total
	Present	Absent	
Female	23 (18.0%)	105 (82.0%)	128 (100.0%)
Male	12 (10.7%)	100 (89.3%)	112 (100.0%)
Total	35 (14.6%)	205 (85.4%)	240 (100.0%)

Female stillborn babies suffered from congenital anomalies than males (Table I).

Risk estimate was calculated between the presence or absence of congenital anomalies and the fetal sex being male or female (Table II).

Table 2
Risk estimate for fetal sex and presence of congenital anomalies

	Value
Odds Ratio for fetal sex (Female / Male)	1.825
For cohort congenital anomaly = Present	1.682
For cohort congenital anomaly = Absent	0.918
N of Valid Cases	**240**

The odds of having of congenital anomalies 1.825 times greater for female stillbirths compared to male stillborn babies (Table II). Relative risk for outcome as congenital anomalies present among stillbirths is 1.682 while relative risk for outcome as absent congenital anomalies was 0.918.

Stillborn fetuses with congenital malformations, deformations, and chromosomal abnormalities were categorized according to their POG at death (Table III).

Table 3
Frequency of stillbirths with congenital anomalies in relation to POG at death and fetal sex

POG (weeks)		Sex of the fetus			Total number of stillbirths (%)
		Male –n (%)	Female–n (%)	Unidentified – n (%)	
Preterm	< 28	6 (2.4)	5 (2.0)	-	11 (4.5)
	28 to < 32	3 (1.2)	6 (2.4)	-	9 (3.7)
	32 to < 37	1 (0.4)	8 (3.3)	1 (0.4)	10 (4.1)
Term	≥ 37	2 (0.8)	4 (1.6)	-	6 (2.4)
Total		12 (4.9)	23 (9.4)	-	36 (14.6)

The least number was reported from gestational age is 37 weeks or greater where the stillborn fetuses reached the term pregnancy (Table III). The highest proportion of the stillbirths fell into the preterm category (N = 30, 12.1%).

To describe this distribution further, OR was calculated between the POG (preterm and term) and the presence of congenital anomalies (present or absent) (Table IV).

Table 4
Risk Estimate between the presence of congenital anomalies and the POG

Presence of congenital anomalies	POG (weeks)		OR	95% CI	
	< 37 (Preterm)	≥ 37 (Term)		**Lower**	**Upper**
Present	30 (18.1%)	6 (8.0%)	2.537	1.008	6.386
Absent	136 (81.9%)	69 (92.0%)			

The risk to be preterm stillbirth for the fetuses with visible structural congenital anomalies was 2.537 times greater than the stillbirths which did not have obvious structural congenital anomalies (Table IV).

The recorded visible structural congenital anomalies were classified according to the blocks of ICD 10 (Q00-Q99). The blocks found in the study were congenital malformations of the nervous system (Q00-Q07); eye, ear, face, and neck (Q10-Q18); the circulatory system (Q20-Q28); cleft lip and cleft palate (Q35-Q37); other congenital malformations of the digestive system (Q38-Q45); congenital malformations of the genital organs (Q50-Q56); congenital malformations and deformations of the musculoskeletal system (Q65-Q79); other congenital malformations (Q80-Q89); and chromosomal abnormalities, not elsewhere classified (Q90-Q99).

The various congenital anomalies that belonged to the above blocks of ICD 10and their frequencies, were presented in Table V.

Table 5
Frequencies of reported visible structural congenital anomalies and their distribution according to the ICD 10 blocks and the sex of the fetus

Block (N, %)	Congenital malformation, deformation, and chromosomal abnormality	ICD Code (Q)	Number (%)		Total Number (%)
			Male	Female	
The nervous system (n = 19, 7.7%)	Anencephaly	00.0	1	8	9 (3.7)
	Craniorachischisis	00.1	-	1	1 (0.4)
	Occipital encephalocele	01.2	-	1	1 (0.4)
	Congenital hydrocephalus	03.8	-	2	2 (0.8)
	Spina bifida	05	-	6	6 (2.4)
Eye, ear, face and neck (n = 2, 0.8%)	Anophthalmos	11.0	1	-	1 (0.4)
	Macrophthalmos	11.3	1	-	1 (0.4)
The circulatory system (n = 1, 0.4%)	Ectopia cordis	24.8	-	1	1 (0.4)
Cleft lip and cleft palate (n = 4, 1.6%)	Cleft soft palate	35.3	1	-	1 (0.4)
	Cleft lip, bilateral	36.0	-	1	1 (0.4)
	Cleft lip, unilateral	36.9	1	-	1 (0.4)
	Cleft hard palate with unilateral cleft lip	37.1	1	-	1 0.4)
Other congenital malformations of the digestive system (n = 1, 0.4%)	Unspecified malformation of the anus (relatively large anal diameter)	45.9	1	-	1 (0.4)
Genital organs (n = 5, 2.0%)	Hypoplasia of penis	55.6	2	-	2 (0.8)
	Malformations of vulva	52.7	-	1	1 (0.4)
	Undescended testicle, bilateral	53.2	1	-	1 (0.4)
	Indeterminate sex, unspecified	56.4	1	-	1 (0.4)
Congenital malformations and deformations of the musculoskeletal system (n = 26, 10.6%)	Facial asymmetry	67.0	2	-	2 (0.8)
	Congenital Clubhand	71.4	-	1	1 (0.4)
	Phocomilia, upper limb	73.1	-	1	1 (0.4)
	Congenital shortening of upper limbs	71.4	-	3	3 (1.2)

Block (N, %)	Congenital malformation, deformation, and chromosomal abnormality	ICD Code (Q)	Number (%)		Total Number (%)
			Male	Female	
	Congenital scoliosis	67.5	-	2	2 (0.8)
	Congenital malformation of the bony thorax (very narrow rib cage)	76.8	1	-	1 (0.4)
	Omphalocele	79.2	1	3	4 (1.6)
	Congenital shortening of lower limbs	72.8	-	3	3 (1.2)
	Congenital talipes equinovarus (CTEV)	66.8	2	4	6 (2.4)
	Achondroplasia	77.4	1	1	2 (0.8)
	Treacher-Collins syndrome	75.4	-	1	1 (0.4)
Other congenital malformations (n = 1, 0.4%)	Micrognathia	87.0	-	1	1 (0.4)
Chromosomal abnormalities, not elsewhere classified (n = 3, 1.2%)	Down syndrome	90	2	1	3 (1.2)

The most frequently affected body system was the musculoskeletal system (n = 26, 10.6%) (Table V). However, the most frequent type of anomaly was *anencephaly* which represented 3.7% of the stillbirth sample followed by *spina bifida* and CTEV (each n = 6, 2.4%). The only chromosomal abnormality that displayed identifiable structural anomalies was Down syndrome (n = 3, 1.2%). Majority of the congenital malformations and deformations affected female stillbirths. Three types of chromosomal abnormalities were observed (Achondroplasia, Down, and Treacher-Collin syndromes).

Discussion

The focal point of this study was to figure out externally visible structural congenital malformations, deformations, and chromosomal abnormalities prevailing in stillbirths. Moreover, the observed congenital anomalies were analyzed to assess their distribution according to the sex of the fetus and POG.

There is no impact of POG for stillborn babies with congenital anomalies in our study. Therefore, it is impossible to predict the exact gestational age for stillbirths to occur either with or without congenital anomalies.

The results revealed nearly 15% of stillbirths presented with either congenital malformations, deformations, or chromosomal abnormalities. This study also revealed that a higher proportion of female

fetuses had congenital anomalies during intrauterine life leading to stillbirths. Globally, 2.4% of births have been found to have congenital anomalies whereas it was 14.6% among stillbirths in our study which indicates a higher percentage of congenital anomalies among stillborn[18]. In an Australian study, it was 27%[24]. A British study reported that 10.5% of stillbirths were affected by congenital anomalies[25].

According to Sunethri et al., (2011) male stillbirths are more prone to congenital anomalies than female stillbirths[26]. In Pat Doyle et al., (2004) study males tend to have congenital malformations than females9[9]. However, our study disclosed the opposite where the frequency of congenital anomalies was about two-fold in females compared to males. The OR was two times greater in females with congenital anomalies than male stillbirths with congenital anomalies.

8.4% of the stillbirths had CNS anomalies in our study which was higher compared to 2.1% in a study by Rankin et al[25]. Whites (5%) and African Americans (2.6%) were found to have higher rates of CNS birth defects than other system[27]. Comparing these results, a higher prevalence of CNS anomalies is seen in our survey. This study found that *anencephaly* was the most frequent anomaly at 4% among all the cases and the majority was female. Wiliams, (1970) also demonstrated that female gender fetuses were more prone to *anencephaly* than male fetuses[28].

Another fact through our research discovered was that the majority of the congenital anomalies of stillborn babies belonged to the musculoskeletal system. However, different results have been reported internationally, with the majority of anomalies arising from CNS, heart, and Down syndrome[18,26,27,29,30].

Ectopiacordis where the fetus's heart located totally outside the thorax, was the only congenital structural cardiac anomaly observed in the current study (n = 1, 0.4%). But worldwide, the prevalence varied. Most of the studies showed higher rates than this except one Indian study that found one (0.98%) stillbirth with *dextrocardia*[25,26,31]. Cleft lip with cleft palate (0.4%) and cleft palate alone (0.4%) was similar to some findings, 0.1%, and 0.3% while it was much lower than others at 23.33%[25,31].

Regarding the POG of stillbirths, this research study revealed that fetuses with congenital anomalies are more prone to turn into preterm stillbirths. According to the results, the risk was about 2.5 times higher than the stillbirths which did not have observable external structural congenital malformations and chromosomal abnormalities.

Conclusion

Externally observable congenital malformations, deformations, and chromosomal abnormalities lead to preterm stillbirths. *Anencephaly* was the most frequent anomaly observed. The number of musculoskeletal malformations and chromosomal abnormalities were greater than other systemic structural anomalies among stillbirths. Female fetuses were at high risk to acquire congenital anomalies than male fetuses.

Abbreviations

CI Confidence interval

CNS Central nervous system

CTEV Congenital talipes equinovarus

d Absolute precision

ICD 10 International Statistical Classification of Diseases and Related Health problems 10th Revision

OR Odds ratio

P Anticipated population

POG Period of gestation

SD Standard deviation

US United States

USG Ultrasonography

WHO World Health Organization

Declarations

Ethical approval and consent to participate

The study was approved by the Ethics Review Committee, Faculty of Medicine, University of Peradeniya (2016/EC/98). The permission was gained from the Directors, medical superintendents of hospitals, consultants obstetricians and gynecologists, consultants pediatricians, nursing sisters, and in-charge nurses and staff members of the antenatal wards, postnatal wards, labor rooms, and operation theatres. Written, informed consent was taken from the mothers who participated in the study to examine the stillborn fetuses.

Consent for publication

All four authors have granted the consent for publication.

Availability of data and material

Data and material will be provided on request if all authors' approved.

Competing interests

The authors do not have conflicting interests.

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Authors’ contributions

AMSS conceived and designed the study, took the lead in writing the manuscript, collected the data, performed data analyzing.

CJR conceived, designed and directed the study, reviewed and enhanced the quality of the manuscript.

KEK conceived, designed and directed the study, reviewed and enhanced the quality of the manuscript.

SBT conceived, designed and directed the study, reviewed and enhanced the quality of the manuscript, Analyzed the data.

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Figures

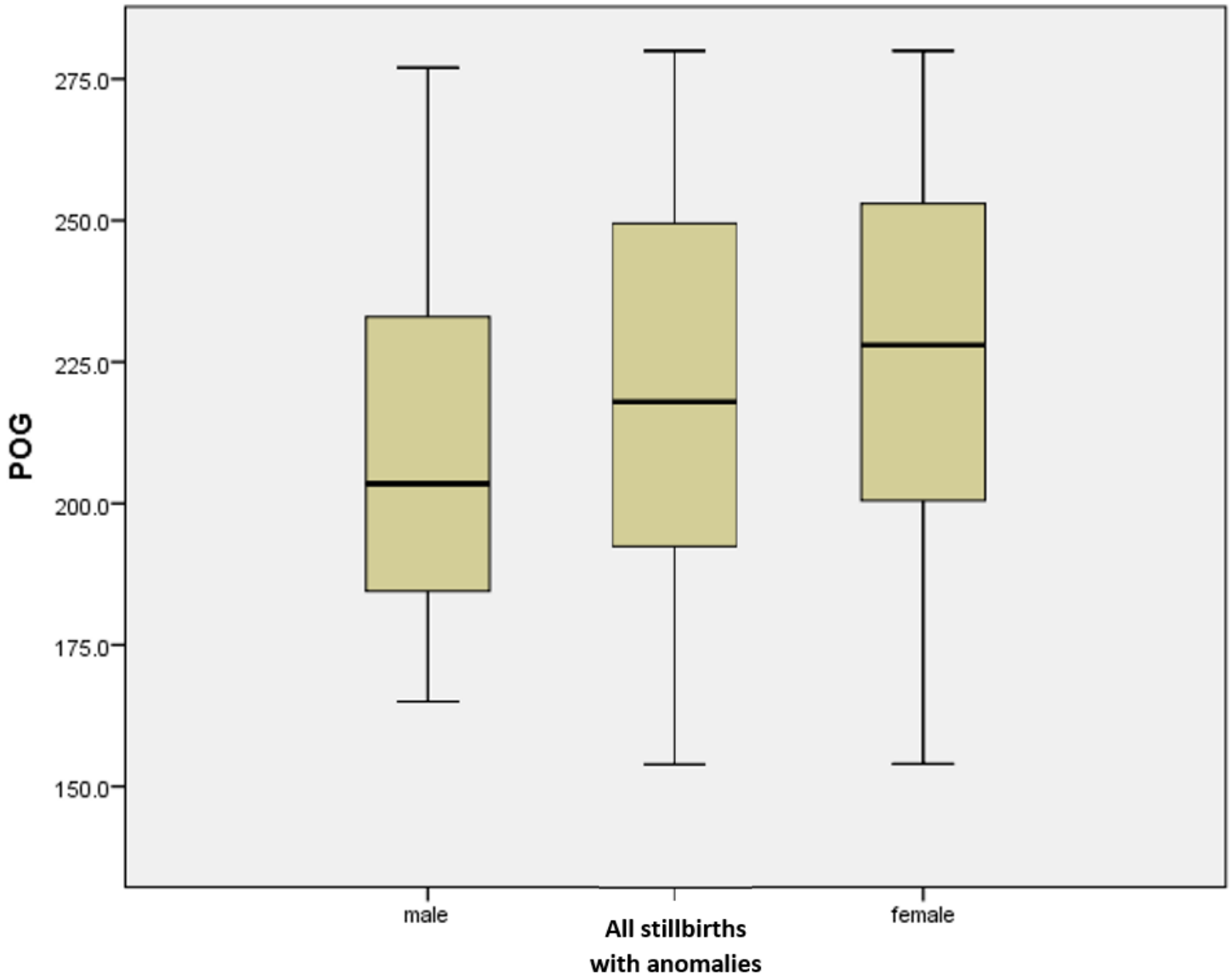

Figure 1

Box and whisker plot of distribution of the POG (days) among the stillbirths with external structural congenital anomalies according to the fetal sex