EUROX 23 (2024) 100338

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology: X

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Epidemiology and placental pathology of intrauterine fetal demise in a tertiary hospital in the Philippines

Ourlad Alzeus G. Tantengco [a,*], Michele H. Diwa [b,c], Patrick Michael M. Millagrosa [a], Clarissa L. Velayo [a,d]

[a] Department of Physiology, College of Medicine, University of the Philippines Manila, Manila, Philippines
[b] Department of Pathology, College of Medicine, University of the Philippines Manila, Manila, Philippines
[c] Department of Laboratories, University of the Philippines - Philippine General Hospital, Taft Avenue, Manila, Philippines
[d] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of the Philippines - Philippine General Hospital, Taft Avenue, Manila, Philippines

ARTICLE INFO

Keywords:
Antenatal care visit
Chorioamnionitis
Miscarriage
Preeclampsia
Stillbirth

ABSTRACT

Objectives: The Philippines has at least 25,000 stillbirth or intrauterine fetal demise (IUFD) cases every year. Despite its burden, there is scarce information on IUFD epidemiology in the Philippines. Hence, this study reported the epidemiology and placental pathology of IUFD in a tertiary hospital in the Philippines.
Study design: This cross-sectional study analyzed second- and third-trimester IUFD cases at the Philippine General Hospital from 2012 to 2021. We reviewed maternal sociodemographic and clinical characteristics and evaluated placental pathology. All statistical tests were done with GraphPad Prism software version 8.0.
Results: We recorded 947 (2.28 %) cases of IUFD out of 41,562 obstetric deliveries from 2012 to 2021. Out of 947 IUFD cases, 532 had placental pathology reports. Second-trimester IUFD cases showed higher rates of no antenatal care (42.86 %) compared to third-trimester cases (10.61 %). Hypertensive disorders were more common in third-trimester IUFD. Infarcts (23.34 %), calcifications (4.12 %), and hemorrhages/hematomas (3.00 %) were the most prevalent placental abnormalities. While these abnormalities were more common in third-trimester IUFD, placental and fetal membrane infections like chorioamnionitis were more frequent in second-trimester IUFD.
Conclusion: The results highlighted the differences in maternal sociodemographic and clinical characteristics, and placental pathology between second- and third-trimester cases of IUFD. These observations revealed distinct pathological processes and potential etiologies contributing to IUFD in the Philippines.

Introduction

Stillbirth is defined variably by WHO, ACOG, and RCOG [1-3]. For this study, we used ACOG's definition: fetal death at ≥ 20 weeks or ≥ 350 g [1-4]. The differences in stillbirth and IUFD definitions, as well as lack of data collection systems, meant that global estimates of IUFD cases do not represent the extent of IUFD worldwide. In 2019, there was an estimated two million cases of stillbirths, following WHO's definition, equivalent to about 13.9 stillbirths per 1000 total births [1]. Variations in stillbirth rates are evident across different regions of the world, from 3.4 per 1000 births in highly developed countries to 36 per 1000 births in developing countries [2]. In the Philippines, with a stillbirth rate of 10.17 in 2021, at least 25,000 stillbirth cases are recorded every year [3,4].

While IUFD is a multifactorial condition, around 76 % of reported cases are of unknown etiologies but may likely be due to maternal factors, fetal and placental factors, stressors, or any combination of the three [5,6]. Assigning the cause of stillbirths remains a challenge, given the myriads of possible factors from either the maternal or fetal side, often influencing one another and making it difficult to identify the actual etiology [7,8]. Arising from the intimate connection between the mother and the fetus are factors like umbilical cord pathology, placental abruption, congenital anomalies and malformations, and chromosomal abnormalities [9]. Beyond these factors, maternal medical conditions have also been found to contribute to IUFD with comorbidities like hypertension, diabetes mellitus, thyroid disorders, and systemic lupus erythematosus [10] as well as syphilis, malaria, and human immunodeficiency virus infections [11].

* Corresponding author.
E-mail address: ogtantengco@up.edu.ph (O.A.G. Tantengco).

https://doi.org/10.1016/j.eurox.2024.100338
Received 27 June 2024; Received in revised form 19 August 2024; Accepted 23 August 2024
Available online 27 August 2024

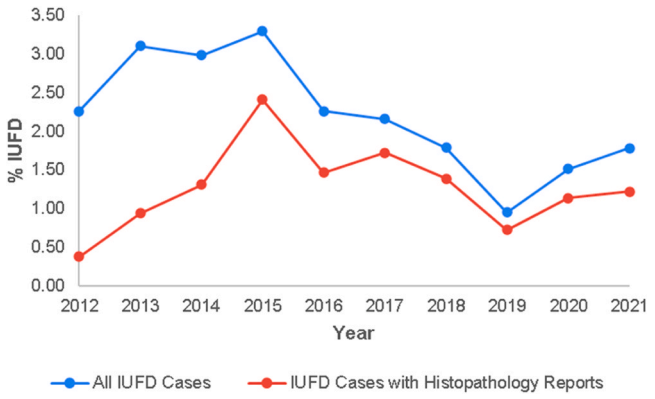

Fig. 1. The annual trends of intrauterine fetal death from 2012 to 2021 in the Philippine General Hospital.

Demographic, environmental, lifestyle, and nutritional factors are also essential contributors to IUFD. These factors are not mutually exclusive and could coincide with each other. Notably, IUFD due to older maternal age (35 years and above) can also be attributed to non-communicable diseases and lifestyle factors. On one note, adolescent pregnancy, and short interpregnancy intervals were also identified as risk factors for IUFD [11]. Furthermore, a higher incidence of IUFD was also found among unbooked cases, primigravida, and women from lower socioeconomic strata, highlighting the need to recognize socio-economic conditions as predisposing factors for IUFD [12].

Across various studies, placental pathology was found to be crucial in explaining the cause of the majority (> 60 %) of stillbirth cases [8]. Despite this observation, histologic examination of the placental is not always performed for all IUFD cases in developing countries [13]. Meanwhile, a systematic review revealed that most diagnoses of placental abnormalities reported in stillbirth studies relied on qualitative, non-specific descriptions. Classification systems for placental abnormalities also vary, as some studies include conditions not fundamentally accepted as exclusively linked to placental causes like chorioamnionitis [14].

Chorioamnionitis has been associated with around 23–37 % of reported IUFD cases [15]. Histologically, evidence of chorioamnionitis tends to decrease as pregnancy progresses. A high incidence of chorioamnionitis across different gestational ages may cause some of the reported IUFD cases [16]. However, chorioamnionitis, described as a maternal inflammatory response, may not be sufficient to cause IUFD alone. With that, it is crucial to evaluate placental and fetal tissues for pathogens, as some cases of IUFD occur in the absence of histological chorioamnionitis [17,18].

Currently, there is insufficient evidence regarding the epidemiology and placental pathology associated with IUFD in the Philippines. Hence, this study determined the maternal sociodemographic and clinical

Fig. 2. The annual trends of intrauterine fetal death in the Philippine General Hospital from 2012 to 2021 based on (A) the trimester of pregnancy and (B) the presence or absence of placental infection.

Table 1
Sociodemographic characteristics of patients with intrauterine fetal death in the Philippine General Hospital from 2012 to 2021.

Indicator	Second trimester		Third trimester		Total	%	p-value
	n	%	n	%			
Antenatal Care Visits							
Booked cases	52	57.14	395	89.57	447	84.02	< .001
Unbooked cases	39	42.86	46	10.43	85	15.98	
Region							
Bicol Region	1	1.10	0	0.00	1	0.19	0.047
CALABARZON	38	41.76	195	44.22	233	43.80	
Central Luzon	1	1.10	9	2.04	10	1.88	
Eastern Visayas	0	0.00	1	0.23	1	0.19	
Ilocos Region	1	1.10	0	0.00	1	0.19	
National Capital Region	49	53.85	234	53.06	283	53.20	
SOCCSKSARGEN	1	1.10	0	0.00	1	0.19	
Western Visayas	0	0.00	1	0.23	1	0.19	
Unknown	0	0.00	1	0.23	1	0.19	
Age	28.23 ± 8.33		28.55 ± 7.28		28.48 ± 7.47		0.710
Marital Status							
Single	55	60.44	288	65.31	343	64.47	0.838
Married	31	34.07	135	30.61	166	31.20	
Widowed	0	0.00	1	0.23	1	0.19	
Unknown	5	5.49	17	3.85	22	4.14	

characteristics of IUFD cases in a tertiary hospital in the Philippines and analyzed for placental pathologies associated with these reported IUFD cases.

Methods

This is a retrospective cross-sectional study of women with second- and third-trimester pregnancy loss at the Philippine General Hospital between 2012 and 2021. The study was approved by the University of the Philippines Manila Research Ethics Board (UPMREB 2023-0334-01). Employing convenience sampling, cases of spontaneous second- and third-trimester pregnancy losses with complete clinical and histopathological data were included. Clinical data collected included maternal demographic profile, prenatal care location, obstetrical history, gestational age, admission diagnosis, intervention, and fetal outcomes.

Results of the placental pathology examinations were retrieved from the Division of Surgical Pathology, Department of Laboratories of the Philippine General Hospital. The information collected included placental weight and dimensions, as well as length, insertion, and vasculature of the umbilical cord. Abnormal cord insertion was defined as either of velamentous or marginal insertion. Pathology examinations followed the institutional protocol, which includes gross and microscopic examination by experienced pathologists. Various microscopic findings like calcifications, hematomas, and infarctions, if present, were also noted.

Data was analyzed with GraphPad Prism software version 8.0. Continuous variables were presented as means with standard deviations or as medians with corresponding interquartile ranges, as appropriate. Categorical variables (nulliparity, fetal sex, PPROM, history of preterm delivery, history of abortion, placental infarction, placental hemorrhages, abnormal cord insertion, and chorioamnionitis) were presented as rates (%). The Shapiro-Wilk test was done to determine the distribution of the data. Continuous parameters were compared by t-test or Mann–Whitney's U test, and categorical variables by Chi-square or Fisher exact test, as appropriate. A p-value of < 0.05 was considered statistically significant.

Results

Annual trends of intrauterine fetal death

We recorded 947 (2.28 %) cases of IUFD out of 41,562 obstetric deliveries from 2012 to 2021. The prevalence of IUFD varied annually, peaking in 2015 at 3.30 % and decreasing to 0.95 % in 2019. However, it started to increase in 2020 and reached 1.78 % in 2021. Of all the IUFD cases, only 532 had comprehensive placental and umbilical cord histopathologic evaluations (Fig. 1).

There were 441 third-trimester cases of IUFD and only 91 second-trimester cases of IUFD. The prevalence of second-trimester cases remained steady, ranging from 0.10 % to 0.51 %. In contrast, the prevalence of third-trimester cases fluctuates annually, increasing until 2015 (81 cases, 1.89 %) and then decreasing until 2019 (27 cases, 0.61 %) (Fig. 2**A**). There are also annual variations in the proportion of placental infections among IUFD cases which increased from 2012 to 2021 when it reached 50 % of IUFD cases (Fig. 2**B**).

Sociodemographic characteristics

Among second-trimester IUFD cases, 42.86 % had no antenatal care visits, compared to 10.61 % of third-trimester cases (Table 1). Most cases were from the National Capital Region and CALABARZON. No significant difference was noted in the mean age of IUFD patients between the second (28.23 ± 8.33 years old) and third trimesters (28.55 ± 7.28 years old) ($p = 0.71$). Most IUFD patients were single, comprising 60.44 % of second-trimester cases and 65.01 % of third-trimester cases (Table 1).

Clinical characteristics

Regarding BMI, there were more underweight (7.69 %) and normal BMI (46.15%) patients among second-trimester IUFD cases, while overweight (20.63 %), obese I (33.33 %), and obese II (13.15 %) patients were predominant among third-trimester IUFD cases ($p < 0.001$). The highest proportion of IUFD cases involved nulliparous women in the second trimester (34.07 %) and multiparous women in the third trimester (35.57 %). Most patients in both trimesters did not have a history of preterm birth. Second-trimester IUFD cases exhibited a higher prevalence of previous abortion (21.98 %) compared to third-trimester cases (14.00 %) (Table 2).

Hypertensive disorders of pregnancy (HDP) and placental disorders were the most common comorbidities. Significantly more third-trimester IUFD patients (19.73 %) had hypertensive disorders of pregnancy compared to second-trimester patients (9.89 %). For the third-trimester IUFD cases, preeclampsia with severe features was the most common HDP with 43 cases (49.43 %), followed by gestational hypertension (20.63 %), and chronic hypertension with superimposed preeclampsia (17.24 %). On the other hand, chronic hypertension (44.4 %) and chronic hypertension with superimposed preeclampsia (44.4 %) were the most common HDP in the second trimester (Table 2).

Cesarean deliveries were more frequent among third-trimester IUFD cases than second-trimester cases ($p < 0.001$). For third-trimester IUFD cases, most did not have reported indications for CS deliveries (45.88 %). The most common indications were deteriorating maternal status (15.29 %), abruptio placenta (8.24 %), and malpresentation (7.06 %). There were only four second-trimester IUFD cases that had CS deliveries. Two cases did not have reported indication for CS delivery; one was due to abruptio placenta, and one case was due to placenta previa. The mean fetal birthweight was 490.55 ± 561.13 g for second-trimester IUFD cases and 1628 ± 922.96 g for third-trimester IUFD cases (Table 2).

Table 2
Clinical characteristics of patients with intrauterine fetal death in the Philippine General Hospital from 2012 to 2021.

Factor	Second trimester		Third trimester		Total	%	p-value
	n	%	n	%			
Body Mass Index							
Underweight	7	7.69	13	2.95	20	3.76	< .001
Normal	42	46.15	111	25.17	153	28.76	
Overweight	14	15.38	91	20.63	105	19.74	
Obese I	16	17.58	147	33.33	163	30.64	
Obese II	5	5.49	58	13.15	63	11.84	
Unknown	7	7.69	21	4.76	28	5.26	
Parity							
Nulliparity	31	34.07	153	34.69	184	34.59	0.129
Single	25	27.47	106	24.04	131	24.62	
Multiparity	26	28.57	156	35.37	182	34.21	
Grand multiparity	8	8.79	24	5.44	32	6.02	
Great grand multiparity	0	0.00	2	0.45	2	0.38	
Unknown	0	0.00	1	0.23	1	0.19	
Preterm Birth							
With a history	11	12.09	40	9.03	51	9.55	0.366
Without history	80	87.91	403	90.97	483	90.45	
Abortion							
With a history	20	21.98	62	14.00	82	15.36	0.054
Without history	71	78.02	381	86.00	452	84.64	
Nature of Pregnancy							
Singleton	86	94.51	426	96.60	512	96.24	0.355
Twin	5	5.49	15	3.40	20	3.76	
Comorbidities							
COVID-19 infection	0	0.00	3	0.68	3	0.56	0.431
Hypertensive disorders	9	9.89	87	19.73	96	18.05	0.027
Diabetes	2	2.20	16	3.63	18	3.38	0.496
Thyroid disorders	2	2.20	9	2.04	11	2.07	0.919
Hepatitis infection	1	1.10	7	1.59	8	1.50	0.731
Respiratory disorders	1	1.10	8	1.81	9	1.69	0.633
Antiphospholipid antibody syndrome	1	1.10	4	0.91	5	0.94	0.860
Reproductive tract disorders	3	3.30	17	3.85	20	3.76	0.805
Placental disorders	4	4.40	38	8.62	42	7.89	0.177
Hydramnios	3	3.30	9	2.04	12	2.26	0.458
Fetal anomalies	1	1.10	27	6.12	28	5.26	0.051
Mode of Delivery							
Cesarean section	4	4.40	82	18.59	86	16.17	< 0.001
Instrument-assisted vaginal delivery	8	8.79	4	0.91	12	2.26	
Vaginal delivery	65	71.43	278	63.04	343	64.47	
Unknown	14	15.38	77	17.46	91	17.11	
Fetal Sex							
Male	12	13.19	85	19.27	97	18.23	0.003
Female	5	5.49	74	16.78	79	14.85	
Unknown	74	81.32	282	63.95	356	66.92	
Fetal birthweight	490.55 ± 561.13 g		1628 ± 922.96 g		1445.39 ± 980.23 g		< 0.001

Placental and umbilical cord pathology

This study included 512 singleton and 20 twin pregnancy patients (Table 3)—third-trimester IUFD cases predominated in both singleton and twin pregnancies. Among IUFD cases in twin pregnancies, monochorionic-diamniotic placentation was the most common (3/5, 60 %) in second-trimester cases and (9/15, 60 %) in third-trimester cases. The most prevalent placental abnormalities were infarcts (Fig. 3**A**) (23.41 %), most of which comprised at least 5 % of the placenta, calcifications (4.14 %), hemorrhages/hematomas (3.19 %), and accelerated villous maturation (1.88 %). Placental abnormalities were generally more common in third-trimester IUFD compared to second-trimester IUFD. However, placental and fetal membrane infections were more frequent in second-trimester IUFD cases. Chorioamnionitis (Fig. 3**B–C**) was observed in 21.98 % of second-trimester IUFD cases and 16.03 % of third-trimester IUFD cases. The most common umbilical cord pathology was funisitis (Fig. 3**D**), observed in 4.4 % of second-trimester IUFD cases and in 4.06 % of third-trimester cases (Table 4).

Discussion

Our study, the largest on IUFD in the Philippines, revealed significant differences in maternal and placental characteristics between second- and third-trimester IUFD cases, highlighting the importance of antenatal care and the role of hypertensive disorders. While the prevalence of IUFD cases were generally decreasing pre-pandemic, it started to increase during the pandemic period. The limitation in mobility due to lockdown and the unavailability of in-person prenatal consultation during the pandemic may have contributed to this increase in IUFD prevalence [19,20]. There was also a contrast between the generally stable prevalence of second-trimester IUFD cases and the decreasing trend on third-trimester cases. This decrease in third-trimester IUFD cases may be attributed to improved management of pregnant patients, most especially high-risk pregnant patients [21].

Our study revealed that 42.86 % of second-trimester IUFD cases and 10.61 % of third-trimester IUFD cases were associated with non-attendance of antenatal care (ANC) visits. The World Health Organization and the Philippine Department of Health emphasized that it is essential that mothers should have at least four prenatal visits to ensure that proper care is observed [22]. Despite an overall increase in ANC utilization in the Philippines from 1993 to 2017, geographical

Table 3
Placental histopathologic findings in patients with intrauterine fetal death in the Philippine General Hospital from 2012 to 2021.

Finding	Second trimester		Third trimester		Total	
	n	%	n	%	n	%
Placental Type						
Singleton						
Immature	59	68.60	96	22.54	155	30.27
Mature	3	3.49	212	49.77	215	41.99
Second Trimester	15	17.44	27	6.34	42	8.20
Third Trimester	3	3.49	81	19.01	84	16.41
Others	6	6.98	10	2.35	16	3.13
Twin						
Monochorionic-Monoamnionic	0	0	2	13.33	2	10
Monochorionic-Diamnionic	3	60	9	60	12	60
Dichorionic-Diamnionic	1	20	3	20	4	20
Others	1	20	1	6.67	2	10
Placental Abnormalities						
Infarcts						
Less than 5 %	7	7.69	11	2.49	18	3.38
At least 5 %	1	1.1	107	24.26	108	20.3
Calcifications						
Microcalcifications	2	2.2	13	2.95	15	2.82
Others	1	1.1	6	1.36	7	1.32
Villous changes						
Accelerated villous maturation	2	2.2	8	1.81	10	1.88
Uneven villous maturations	0	0	3	0.68	3	0.56
Villous edema	0	0	2	0.45	2	0.38
Villous hypoplasia	0	0	2	0.45	2	0.38
Villous dysmaturity	0	0	1	0.23	1	0.19
Villous fibrosis	0	0	2	0.45	2	0.38
Villous fibrin depositions	1	1.1	4	0.91	5	0.94
Others						
Hemorrhages	0	0	14	3.17	14	2.63
Hematomas	1	1.1	2	0.45	3	0.56
Erythroblastosis	1	1.1	3	0.68	4	0.75
Erythrocytosis	0	0	1	0.23	1	0.19
Placentomegaly	0	0	6	1.36	6	1.13
Degenerative changes	1	1.1	8	1.81	9	1.69
Hydropic changes	0	0	2	0.45	2	0.38
Autolytic changes	0	0	1	0.23	1	0.19
Meconium staining	0	0	4	0.91	4	0.75
Syncytial knotting	0	0	2	0.45	2	0.38
Schistosomiasis	0	0	1	0.23	1	0.19
Congestion	0	0	1	0.23	1	0.19
Arteriopathy	0	0	1	0.23	1	0.19
Accessory lobe	0	0	1	0.23	1	0.19
Placental Infections						
Chorioamnionitis	20	21.98	71	16.03	91	17.04
Chorionitis	6	6.59	30	6.77	36	6.74
Deciduitis	0	0.00	1	0.23	1	0.19
Focal acute inflammation	0	0.00	1	0.23	1	0.19
Villitis/Villositis	1	1.10	3	0.68	4	0.75

disparities persist. Women residing in remote areas and provinces exhibit lower rates of ANC utilization [23]. Furthermore, the COVID-19 pandemic exacerbated the situation by leading to deferred ANC visits due to lockdown measures, transportation constraints, and financial difficulties [24]. The combination of low ANC utilization and barriers to attendance may heighten the risk of adverse pregnancy outcomes, including fetal death, in the Philippines.

Previous research has underscored the importance of ANC visits in reducing the risk of adverse pregnancy outcomes. A study conducted in Ghana found that early ANC visits were associated with a 43 % reduction in miscarriage risk [25]. Similarly, a study in Finland revealed that inadequate or non-attendance of ANC visits was significantly linked to a higher incidence of fetal deaths (odds ratio: 12.05; 95 % confidence interval: 5.95–24.40) [26]. A meta-analysis corroborated these findings, indicating that fewer ANC visits corresponded to an increased risk of perinatal death (relative risk: 1.14; 95 % confidence interval: 1.00–1.31) [27].

In this study, we reported that hypertensive disorders of pregnancy were the most common comorbidities among IUFD cases. This observation has been widely documented in literature. A population-based study in Canada, including 135,466 pregnancies, reported the risk of stillbirth among births to women with hypertensive disorders of pregnancy [28]. Women with any hypertension in pregnancy were 1.4 (95 % CI 1.1–1.8) times more likely to have a stillbirth as compared with normotensive women. A population-based study in Norway, including 2, 121,371 pregnancies, showed that preeclampsia (aRR: 2.29; 95 % CI: 2.16–2.43), gestational hypertension (aRR: 1.46; 95 % CI: 1.32–1.61), and chronic hypertension (aRR: 2.29; 95 % CI: 1.71–2.63) were associated with increased risks of fetal death [29]. Another study in China showed a weighted stillbirth rate of 21.9 per 1000 births in women with hypertensive disorders of pregnancy. The risk was higher in those who had received fewer antenatal care visits [30].

Abnormal invasion of the spiral arteries by cytotrophoblast cells is observed among preeclampsia patients [31]. Defective deep placentation is usually associated with “greater obstetrical syndromes (GOS)”, which include preeclampsia, intrauterine growth restriction, preterm labor, preterm premature rupture of membranes, late spontaneous abortion, and abruptio placentae [32]. Placental infarcts were documented in approximately 40 % of mild preeclampsia and 70 % of severe preeclampsia in this study. Significant infarcts involving more than 5 % of the placenta were also observed in 39 % of patients with severe preeclampsia. This association is mainly due to the occlusion of spiral arteries by thrombi, strangulation of the placental villi due to increased perivillous or intervillous fibrin deposition, and impairment of fetal circulation due to fetal thrombotic vasculopathy [33]. A previous study showed that placental infarction is the most frequent cause of death, with a perinatal mortality of 2.26 per 1000 births [34]. Placental hemorrhage and hematoma were also observed in IUFD cases in our study. Sonographically detected subchorionic hematoma is associated with an increased risk of miscarriage during the first 20 weeks of gestation [35]. A meta-analysis involving 1132 women with intrauterine hematomas showed that it can increase the risk of spontaneous abortion, preterm birth, fetal growth restriction, and placental abruption [36]. Another study showed that intrauterine hematomas may not increase the risk of first-trimester miscarriage but can increase the risk of preterm birth [37].

The prevalence of chorioamnionitis was 21.98 % among second-trimester IUFD cases and 16.03 % among third-trimester IUFD cases. A study in an urban hospital in the US showed a 56.7 % prevalence of acute chorioamnionitis among second-trimester pregnancy loss patients [38]. Another local study in Turkey showed a 64.7 % prevalence of histological chorioamnionitis in unexplained second-trimester pregnancy loss patients [39]. It was previously observed that chorioamnionitis is a more common cause of second-trimester than third-trimester pregnancy loss [40,41]. Generally, the frequency of histologic chorioamnionitis is usually higher in preterm than term gestations. The reason for this reduction in intrauterine infection with increasing gestation remains unclear. The microbial invasion of the amniotic cavity in term pregnancy is often a result of labor or rupture of the fetal membranes and occurs during this process. In contrast, infection and inflammation usually precede fetal death by promoting massive fetal inflammation in second-trimester pregnancy. This inflammatory response is called the fetal inflammatory response syndrome (FIRS). FIRS is characterized by elevated fetal plasma IL-6 concentration due to the activation of the fetal innate immune system by microbial invasion. FIRS is usually associated with multi-systemic involvement, resulting in higher neonatal morbidity and mortality [42]. However, this fetal response is more often seen after 20 weeks, suggesting that maturation of the fetal inflammatory response is needed to induce fetal death [43].

Conclusion

To our knowledge, this is the first and largest study on the epidemiology and placental pathology of IUFD in the Philippines. This study

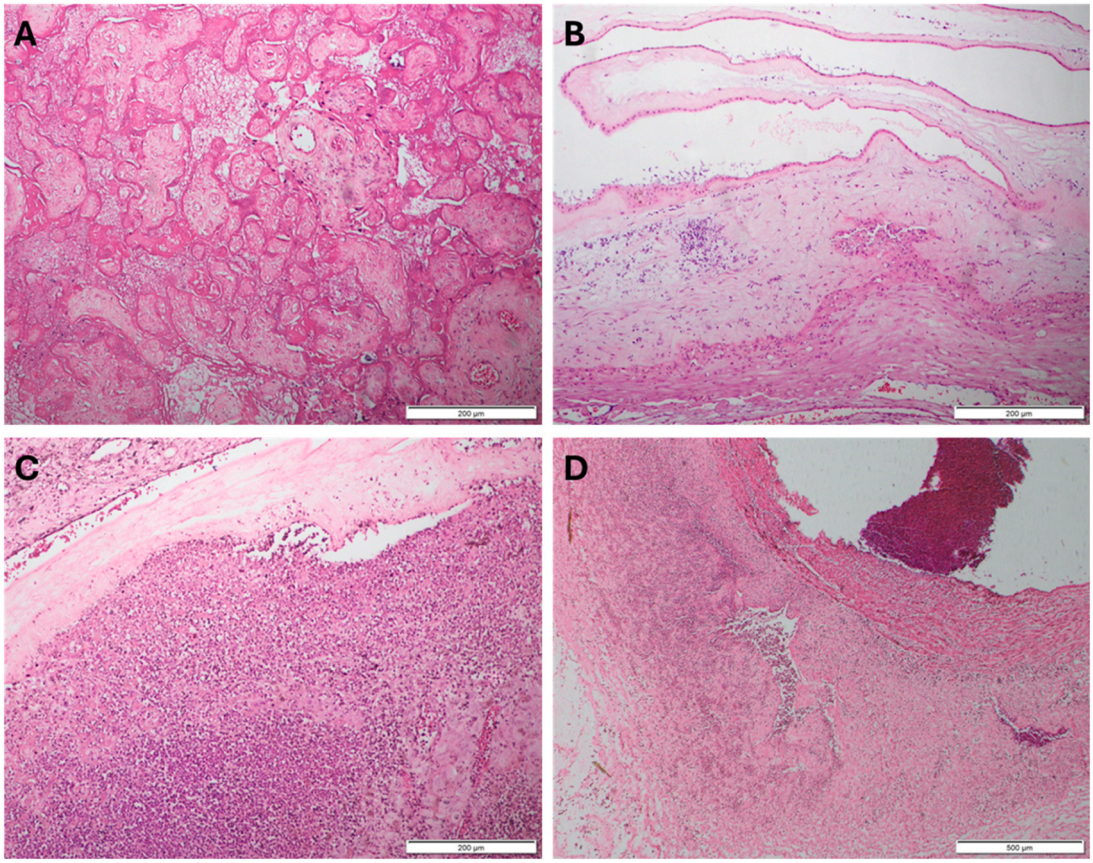

Fig. 3. Histopathologic images of placental and umbilical cord pathologies seen among IUFD cases: A) Villous infract, remote, 100 ×; B) Acute chorioamnionitis, stage 2, grade 1, 100 ×.; C) Acute chorioamnionitis, stage 2, grade 2, 100 ×; D) Acute funisitis, stage 3, grade 2, 40 ×.

Table 4
Umbilical cord histopathologic findings in patients with intrauterine fetal death in the Philippine General Hospital from 2012 to 2021.

	Second trimester		Third trimester			
Finding	n	%	n	%	Total	%
Umbilical Cord Vascularity						
Three Vessel	80	87.91	422	95.69	502	94.36
Two Vessel	0	0.00	8	1.81	8	1.50
No Specimen	11	12.09	11	2.49	22	4.14
Umbilical Cord Abnormality						
Funisitis	4	4.40	18	4.06	22	4.12
Hypercoiling	0	0.00	3	0.68	3	0.56
Necrosis	0	0.00	2	0.45	2	0.37
Stenosis	0	0.00	1	0.23	1	0.19
Hematoma	0	0.00	1	0.23	1	0.19
Autolytic changes	0	0.00	2	0.45	2	0.37
Calcification	0	0.00	1	0.23	1	0.19
Cysts	1	1.10	0	0.00	1	0.19

highlights the importance of antenatal care and identifies hypertensive disorders and placental pathology as significant contributors to IUFD. Different risk factors play a huge role in causing IUFD among second- and third-trimester pregnancies. Further research is needed to explore the etiologies and develop preventive measures. Larger multicenter studies utilizing a prospective cohort study design may provide more information on the significant risk factors and predictors of IUFD in the Philippines.

CRediT authorship contribution statement

Ourlad Alzeus Tantengco: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Clarissa Velayo:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Patrick Michael Millagrosa:** Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Michele Diwa:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Authors Contribution

OAGT, MHD, and CLV conceptualized the study. PMMM and OAGT performed the chart review, analyzed the data, and drafted the manuscript. MHD and CLV helped analyze and interpret the data and write the manuscript. All authors read and approved the final manuscript.

Funding

This study was funded by the faculty research grant awarded to Dr. Michele H. Diwa from the UPM National Institutes of Health.

Declaration of Competing Interest

The authors state no conflicts of interest regarding this study.

References

[1] World Health Orgnization. Stillbirth; 2024. ⟨https://www.who.int/health-topics/stillbirth#tab=tab_1⟩ [Accessed 1 June 2024].

[2] Martin JA, Hoyert DL. The national fetal death file. Semin Perinatol 2002;26:3–11. https://doi.org/10.1053/sper:2002.29834.

[3] Royal College of Obstetricians and Gynaecologists. Late intrauterine fetal death and stillbirth: green–top guideline no. 55, RCOG Green-Top Guideline No. 55; 2010. 32.

[4] Stanton C, Lawn JE, Rahman H, Wilczynska-Ketende K, Hill K. Stillbirth rates: delivering estimates in 190 countries. Lancet 2006;367:1487–94. https://doi.org/10.1016/S0140-6736(06)68586-3.

[5] Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. Lancet 2021;398:772. https://doi.org/10.1016/S0140-6736(21)01112-0.

[6] Blencowe H, Cousens S, Jassir FB, Say L, Chou D, Mathers C, et al. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. Lancet Glob Health 2016;4:e98–108. https://doi.org/10.1016/S2214-109X(15)00275-2.

[7] Stillbirth rate (per 1000 total births); n.d. ⟨https://www.who.int/data/gho/data/indicators/indicator-details/GHO/stillbirth-rate-(per-1000-total-births)⟩. [Accessed 29 March 2024].

[8] Takita H, Hasegawa J, Nakamura M, Arakaki T, Oba T, Matsuoka R, et al. Causes of intrauterine fetal death are changing in recent years. J Perinat Med 2018;46:97–101. https://doi.org/10.1515/JPM-2016-0337/MACHINEREADABLECITATION/RIS.

[9] A child or youth died once every 4.4 s in 2021 – UN report; n.d. ⟨https://www.unicef.org/philippines/press-releases/child-or-youth-died-once-every-44-seconds-2021-un-report⟩ [Accessed 29 March 2024].

[10] Reinebrant HE, Leisher SH, Coory M, Henry S, Wojcieszek AM, Gardener G, et al. Making stillbirths visible: a systematic review of globally reported causes of stillbirth. BJOG 2018;125:212–24. https://doi.org/10.1111/1471-0528.14971.

[11] Warland J, Mitchell EA. A triple risk model for unexplained late stillbirth. BMC Pregnancy Childbirth 2014;14:142. https://doi.org/10.1186/1471-2393-14-142.

[12] Monasta L, Giangreco M, Ancona E, Barbone F, Bet E, Boschian-Bailo P, et al. Retrospective study 2005–2015 of all cases of fetal death occurred at $\geq$ 23 gestational weeks, in Friuli Venezia Giulia, Italy. BMC Pregnancy Childbirth 2020;20. https://doi.org/10.1186/S12884-020-03074-9.

[13] Liu L-C, Huang H-B, Yu M-H, Su H-Y. Analysis of intrauterine fetal demise—a hospital-based study in Taiwan over a decade. Taiwan J Obstet Gynecol 2013;52:546–50. https://doi.org/10.1016/j.tjog.2013.10.016.

[14] Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet 2016;6736:1–17. https://doi.org/10.1016/S0140-6736(15)00837-5.

[15] Dave A, Patidar R, Goyal S, Dave A. Intrauterine fetal demise-a tragic event: a study of its epidemiology, causes and methods of induction. Int J Reprod Contracept Obstet Gynecol 2016;5:1316–21. https://doi.org/10.18203/2320-1770.IJRCOG20161008.

[16] Flenady V, Frøen JF, Pinar H, Torabi R, Saastad E, Guyon G, et al. An evaluation of classification systems for stillbirth. BMC Pregnancy Childbirth 2009;9:1–13. https://doi.org/10.1186/1471-2393-9-24/TABLES/2.

[17] Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. Lancet 2011;377:1703–17. https://doi.org/10.1016/S0140-6736(11)60064-0.

[18] Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AEP. Systematic review of placental pathology reported in association with stillbirth. Placenta 2014;35:552–62. https://doi.org/10.1016/J.PLACENTA.2014.05.011.

[19] Liu L-C, Wang Y-C, Yu M-H, Su H-Y. Major risk factors for stillbirth in different trimesters of pregnancy—a systematic review. Taiwan J Obstet Gynecol 2014;53:141–5. https://doi.org/10.1016/j.tjog.2014.04.003.

[20] Amir H, Weintraub A, Aricha-Tamir B, Apel-Sarid L, Holcberg G, Sheiner E. A piece in the puzzle of intrauterine fetal death: pathological findings in placentas from term and preterm intrauterine fetal death pregnancies. J Matern-Fetal Neonatal Med 2009;22:759–64. https://doi.org/10.3109/14767050902929396.

[21] Manocha A, Ravikumar G, Crasta J. Placenta in intrauterine fetal demise (IUFD): a comprehensive study from a tertiary care hospital. J Matern-Fetal Neonatal Med 2019;32:3939–47. https://doi.org/10.1080/14767058.2018.1479390.

[22] Carter SWD, Neubronner S, Su LL, Dashraath P, Mattar C, Illanes SE, et al. Chorioamnionitis: an update on diagnostic evaluation. Biomedicines 2023;11. https://doi.org/10.3390/BIOMEDICINES11112922.

[23] Mohan M, Appiah-Sakyi K, Oliparambil A, Pullattayil AK, Lindow SW, Ahmed B, et al. A meta-analysis of the global stillbirth rates during the COVID-19 pandemic. J Clin Med 2023;12. https://doi.org/10.3390/jcm12237219.

[24] Dandona R, Kumar GA, Akbar M, Dora SSP, Dandona L. Substantial increase in stillbirth rate during the COVID-19 pandemic: results from a population-based study in the Indian state of Bihar. BMJ Glob Health 2023;8. https://doi.org/10.1136/bmjgh-2023-013021.

[25] Menezes EV, Yakoob MY, Soomro T, Haws RA, Darmstadt GL, Bhutta ZA. Reducing stillbirths: prevention and management of medical disorders and infections during pregnancy. BMC Pregnancy Childbirth 2009;9:S4. https://doi.org/10.1186/1471-2393-9-S1-S4.

[26] Lavado RF, Lagrada LP, Ulep VGT, Tan LM. Who provides good quality prenatal care in the Philippines ?. Makati City; 2010.

[27] Tantengco OAG, Ornos EDB. Trends in health insurance and antenatal care coverage in the Philippines. J Public Health 2023;45:e146–7. https://doi.org/10.1093/PUBMED/FDAC068.

[28] de Guzman GS, Banal-Silao MJB. Antenatal care utilization during the COVID-19 pandemic: an online cross-sectional survey among Filipino women. BMC Pregnancy Childbirth 2022;22:1–12. https://doi.org/10.1186/S12884-022-05234-5/TABLES/5.

[29] Ahmad AS, Samuelsen SO. Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2,121,371 pregnancies. BJOG 2012;119:1521–8. https://doi.org/10.1111/J.1471-0528.2012.03460.X.

[30] Xiong T, Mu Y, Liang J, Zhu J, Li X, Li J, et al. Hypertensive disorders in pregnancy and stillbirth rates: a facility-based study in China. Bull World Health Organ 2018;96:531. https://doi.org/10.2471/BLT.18.208447.

[31] Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Pre-eclampsia: pathophysiology, diagnosis, and management. Vasc Health Risk Manag 2011;7:467–74. https://doi.org/10.2147/vhrm.s20181.

[32] Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol 2011;204:193–201. https://doi.org/10.1016/j.ajog.2010.08.009.

[33] Predoi CG, Grigoriu C, Vladescu R, Mihart AE. Placental damages in preeclampsia–from ultrasound images to histopathological findings. J Med Life 2015;8:62–5.

[34] Naeye RL. Placental infarction leading to fetal or neonatal death. A prospective study. Obstet Gynecol 1977;50:583–8. ⟨http://europepmc.org/abstract/MED/909664⟩.

[35] Kulkarni AD, Palaniappan N, Evans MJ. Placental pathology and stillbirth: a review of the literature and guidelines for the less experienced. J Fetal Med 2017;4(4):177–85. https://doi.org/10.1007/S40556-017-0133-3.

[36] Şükür YE, Göç G, Köse O, Açmaz G, Özmen B, Atabekoğlu CS, et al. The effects of subchorionic hematoma on pregnancy outcome in patients with threatened abortion. J Turk Ger Gynecol Assoc 2014;15:239–42. https://doi.org/10.5152/jtgga.2014.14170.

[37] Qin ZJ, Xu Y, Du Y, Chen YL, Sun L, Zheng A. Intrauterine hematoma in the first trimester and pregnancy complications: a systematic review and meta-analysis. Front Med 2022;9:892146. https://doi.org/10.3389/FMED.2022.892146/BIBTEX.

[38] Al-Memar M, Vaulet T, Fourie H, Bobdiwala S, Farren J, Saso S, et al. First-trimester intrauterine hematoma and pregnancy complications. Ultrasound Obstet Gynecol 2020;55:536–45. https://doi.org/10.1002/UOG.20861.

[39] Heller DS, Moorehouse-Moore C, Skurnick J, Baergen RN. Second-trimester pregnancy loss at an urban hospital. Infect Dis Obstet Gynecol 2003;11:117–22. https://doi.org/10.1080/10647440300025508.

[40] Atay GA, Arsan S, Atasay B, Ensari A, Aysev D. The possible role of intrauterine infections in unexplained second trimester abortions and macerated stillbirths: a study from a single center. J Perinatol 2004;24(11):679–85. https://doi.org/10.1038/sj.jp.7211167.

[41] Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500–7. https://doi.org/10.1056/NEJM200005183422007.

[42] Rudbeck Røge H, Henriques U. Fetal and perinatal infections: a consecutive study. Pathol Res Pr 1992;188:135–40. https://doi.org/10.1016/S0344-0338(11)81169-6.

[43] Jung E, Romero R, Yeo L, Diaz-Primera R, Marin-Concha J, Para R, et al. The fetal inflammatory response syndrome: the origins of a concept, pathophysiology, diagnosis, and obstetrical implications. Semin Fetal Neonatal Med 2020;25:101146. https://doi.org/10.1016/j.siny.2020.101146.