Investigating in utero fetal death outcome of internal medicine consultation

Nicolas Belhomme, Marine Le Noir de Carlan, Alain Lescoat, Thomas Le Gallou, Florence Rouget, Philippe Loget, Patrick Jego

Investigating In Utero Fetal Death: outcome of the internal medicine consultation.

Journal:	International Journal of Rheumatic Diseases
Manuscript ID	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	BELHOMME, Nicolas; Centre Hospitalier Universitaire de Rennes, Médecine Interne Le Noir De Carlan, Marine; Centre Hospitalier Universitaire de Rennes, Médecine Interne Lescoat, Alain; Centre Hospitalier Universitaire de Rennes, Médecine Interne; INSERM, IRSET, UMR 1085, Rennes, France Le Gallou, Thomas; Centre Hospitalier Universitaire de Rennes, Médecine Interne Rouget, Florence; Centre Hospitalier Universitaire de Rennes, Pédiatrie; INSERM, IRSET, UMR 1085, Rennes, France; Réseau Périnatal 35 Loget, Philippe; Centre Hospitalier Universitaire de Rennes, Anatomopathologie Jego, Patrick; Centre Hospitalier Universitaire de Rennes, Médecine Interne; INSERM, IRSET, UMR 1085, Rennes, France
Keywords:	Clinical aspects < Anti-phospholipid antibody syndrome, Drug treatment < Anti-phospholipid antibody syndrome, Epidemiology < Anti-phospholipid antibody syndrome

Title page

Investigating In Utero Fetal Death: outcome of the internal medicine consultation.

Nicolas Belhomme[θ1] M.D., Marine Le Noir de Carlan[1] M.D., Alain Lescoat[2] M.D., Tomas Le Gallou[1] M.D., Florence Rouget[3] M.D., Philippe Loget[4] M.D., Patrick Jego[2] M.D., Ph.D.

[θ]Corresponding author:

Nicolas Belhomme

Department of Internal Medicine, CHU Rennes; University of Rennes 1

2, rue Henri Le Guilloux, 35 000 Rennes, France

Email: nicolas.belhomme@chu-rennes.fr. Tel:+332 99 28 43 21

Affiliations:

[1] Department of Internal Medicine, CHU Rennes, Rennes, France; University of Rennes 1, France.

[2]Department of Internal Medicine, CHU Rennes, Rennes, France ; INSERM, IRSET, UMR 1085, Rennes, France

[3]INSERM, IRSET, UMR 1085, Rennes, France; Department of Pediatrics, CHU Rennes, Rennes, France.

[4]Department of pathology, CHU Rennes, Rennes, France.

Running title: Placenta related fetal death.

Nicolas Belhomme and Marine Le Noir de Carlan wrote the manuscript; Alain Lescoat and Florence Rouget performed the statistical analyzis, Philippe Loget provided the pictures and contributed to the pathological data record, Thomas Le Gallou and Patrick Jego supervised and proofread the manuscript.

Acknowledgements: the authors are indebted to Mrs Gaëlle Belhomme for her help in writing the manuscript.

ABSTRACT

Aim: The objectives were to determine the frequency of in utero fetal death (IUFD) related to placental disorders and to assess the frequency of antiphospholipid antibodies syndrome (APS) among women referred to the internal medicine department.

Methodology: A retrospective clinical study conducted in Rennes University Hospital, France.

Results: From January 2007 to December 2014, 53 women who presented an IUFD at 14 weeks or more of gestational age were included. The main cause for each IUFD was determined by expert agreement. Primary outcome was the prevalence of IUFD related to placental disorders. Secondary outcomes included the frequency of antiphospholipid antibodies syndrome (APS) among patients with IUFD of placental origin and the pathological and clinical features associated to APS. IUFD resulted from placental disorders in 36/53 (68%) patients, and remained unexplained in 11 cases (20.8%). Among the 36 patients with placental disorders, APS was diagnosed in 5 (13.9%) cases, and 4(11.1%) patients were considered as having “non-criteria” APS. History of thrombosis (p=0.001) and placental infarcts (p=0.047) were significantly associated to APS.

Conclusion: Placental disorders were the major cause for IUFD in patients who were referred to internal medicine specialists. Importantly, APS was seldom found in patients with placental disorders. Venous thromboembolism history and placental infarcts were both significantly associated to APS. Further studies are needed in order to deepen our understanding of the physiopathology of placental disorders and its underlying causes among non-APS women, and to determine the best treatment regimen for future pregnancies.

Abbreviations: IUFD= In Utero Fetal Death. APS= Antiphospholipid Antibodies Syndrome.

Keywords: in utero fetal death, stillbirth, internal medicine, placental pathology, antiphospholipid antibodies syndrome, placental vascular disorders

Tweetable abstract: a study analyzing the prevalence of fetal death related to placental disorders in internal medicine.

INTRODUCTION

There is currently no international consensus on the gestational age threshold which defines In Utero Fetal Death (IUFD). The French National College of Gynecologists and Obstetricians (CNGOF) defines IUFD as a spontaneous cessation of fetal cardiac activity occurring before or during labor, after 14 weeks of amenorrhea [1], whereas the threshold of either 22 or 28 weeks or more is commonly used in many countries.[2 3]

Bukowski et al [4] showed that obstetric complications, placental disease, genetic abnormality and infections, were involved in respectively 29%, 26%, 13% and 13% of IUFD, then followed by cord abnormalities (10.4%), hypertensive disorders (9.2%), and maternal complications (7.8%). IUFD were considered idiopathic in 24% of cases.

The objectives of IUFD investigations are to identify the cause, to prepare for future pregnancies, and to detect a maternal pathology requiring specific care, such as antiphospholipid antibodies syndrome (APS).[1]

APS diagnosis requires the presence of clinical and biological criteria meeting the Sydney classification criteria.[5] However, many patients, while fulfilling the clinical criteria, cannot be classified as having APS either because of low titers or non-persistent positivity of conventional antibodies, or because of the detection of other antibodies that have currently not been validated (eg anti-prothrombin…): in those cases, the appellation of “non-criteria” APS is sometimes used.[6 7]

Study objectives

The objectives of our study were to bring to light the internist's role in the diagnosis of IUFD by 1) analyzing the final etiologies diagnosed, on which depend the treatments that will be proposed for future pregnancies 2) evaluating the prevalence of IUFD consecutive to placental vascular disorders 3) assessing the prevalence of APS among these patients and comparing their clinical and pathological features to non-APS patients, in order to find out relevant factors that support APS testing.

METHODS

All women who consulted in the internal medicine department of Rennes University hospital, a French tertiary care center, after IUFD (defined as death at 14 weeks of gestation or later according to the CNGOF) were retrospectively included between January, 1st 2007 and December, 31st 2014. All cases of IUFD were reviewed by four specialists (a pediatrician, a pathologist specialised in foetopathology, an obstetrician and an internist) and the main cause of death was determined through consensual agreement.

According to the Amsterdam Placental Workshop Group Consensus Statement [8], the following histological features were recorded from the pathological records: placental infarcts, retroplacental hematoma, hypotrophia, decidual arteriopathy, fetal vascular malperfusion, thrombosis, villitis, intervillitis, and cord abnormalities. IUFD were classified as placenta-related if the lesions observed were deemed sufficient to lead to fetal death.

APS testing results were recorded for all patients, and obstetrical APS was diagnosed according to Sydney criteria. Clinical and pathological characteristics of patients with APS, “non-criteria” APS and no APS were compared. Patients with APS were classified in the “maternal cause” category according to the CODAC classification[9], and they were also considered as placenta-related IUFD if their placentas exhibited significant lesions.

Statistical methods

Categorical variables associations were analyzed by conducting a Chi square or Fisher exact test. Quantitative data was analyzed by conducting student or Mann and Whitney U test. We performed all tests with a significance level of $P<0.05$. Statistical analyzis was performed using SPSS 20.0 software.

This study was approved by the ethics committee of Rennes University Hospital.

RESULTS

Patients' characteristics

53 patients consulted in internal medicine for IUFD, all of whom were referred by their obstetrician. 22 patients (42%) were primigravida, 5 patients (9%) had a history of IUFD, 9 patients (17%) had a history of miscarriage, 2 patients had an antecedent of preeclampsia, 2 patients an antecedent of HELLP syndrome. A history of severe fetal growth restriction (<5 percentile) was mentioned in two cases. One patient suffered from chronic hypertension, no patients had diabetes mellitus and none had renal disease. 9 patients (13%) were overweight or obese. Three patients were known to have APS, revealed in all cases by venous thrombo-embolism (VTE). APS was considered as primary in all cases as none of our patient had associated connective tissue disease. The patients' mean age at the time of IUFD was of 30 +/- 4.5 years (extremes: 19-42). The mean term was 29.2 weeks of amenorrhea +/- 7.9 (extremes 15-40). There were no multiple pregnancies. Distribution of IUFD according to gestational age is shown in Figure 1.

At the time of IUFD, 7/53 (13%) patients were receiving anticoagulant therapy or antiplatelet agents: 4 patients were treated with low dose aspirin (LDA), because of previous fetal loss in 3 cases, and of severe fetal growth restriction in one case. The three patients with known APS were receiving LDA combined with low-molecular-weight heparin (LMWH).

Biology

Conventional APL (LA, aCL and β2-GPI) were tested in 49/53 patients (90%), and were positive in 9 (17%) cases.

Among the 9 APL positive patients, 8 underwent repeat testing 12 weeks later. Among them, 5 still tested positive: they were classified as having definite APS. The four other patients presented “non-criteria” APS: one of them was tested positive for LA without confirmation 12 weeks apart and presented low titers aCL, the 3 others were negative for conventional APL, but tested positive for anti-prothrombin antibodies.

Pathological findings

A placental histological analyzis was performed in 49/53 cases (92%). Anomalies were found in 40/49 (81%) of the placentas.

Vascular disorders were noted in 33/49 (73%) placentas. Retroplacental hematoma was found in 10 cases, infarcts in 19 cases. Thrombosis were observed in 2 cases, decidual arteriopathy was found in 3 cases. Fetal vascular malperfusion was observed in 7 patients, only one of whom had gestational diabetes. Inflammatory disorders were found in 3 cases: 2 cases of villitis and one case of intervillitis, in all of which TORCH (Toxoplasmosis, Rubella, CMV and Herpes virus) screening was negative. IUFD was related to cord anomaly in 4 cases: cord thrombosis in 3 cases, and tight loops in one case.

All the placentas of the 9 APL positive patients (definite and “non-criteria” APS) were examined: all presented vascular disorders, which associated hypotrophy (constant) with decidual arteriopathy in one case, infarcts in 8/9 cases, retroplacental hematoma in 2 cases, and thrombi in two cases. In one patient was noted the co-existence of fetal vascular malperfusion.

Results of the consultation

The main causes of IUFD are reported in Table 1. Etiological categories were extracted from the CODAC classification[9]: 6 cases issued from maternal causes, including the 5 definite APS patients plus one patient whose IUFD was secondary to severe pre-eclampsia. IUFD of "non-criteria" (n=4) and non-APS patients (n=27) were ruled as having a placental cause. IUFD resulted from placental disorders in 36/53 (68%) patients: placental insufficiency in 33 (62%) cases (including one case of pre-eclampsia), and placental inflammatory disorders in 3 (6%) cases (Table 1). None of our patients had isolated gestational hypertension, renal disease or connective tissue disease.

IUFD was caused by fetal anemia in one case which was classified as a fetal cause, by Parvovirus B19 infection in one case, and by funicular pathology in 4 cases.

IUFD remained unexplained in 11/53 (21%) cases, including all the patients whose placenta was not examined.

Comparison between APS, "non-criteria" APS and non-APS patients

The 36 patients who had significant placental disorders were allocated to one of the following groups according to their APS status: definite APS, "non-criteria" APS and non-APS (in which the patient with pre-eclampsia was included as her placenta exhibited hypotrophia along with massive infarct and retroplacental hematoma).

Only the three patients with known APS had VTE history. Comparisons between the three groups revealed that antecedent of VTE (p=0.001) and placental infarcts (p=0.047) were significantly associated with the definite APS group, whereas fetal vascular malperfusion or inflammatory disorders (villitis/ intervillitis) were not. Patients with "non-criteria" APS were not different from non-APS patients regarding VTE history or pathological findings.

There were no differences in mothers' age, time of pregnancy termination, presence of livedo, history of fetal loss, or placental hypotrophia, between the 3 groups.

DISCUSSION

53 cases of IUFD were referred to an internist over the study period. In the meantime, 440 cases were registered in our center, meaning that internists were consulted in 12% of cases. Placental disorders were over represented, as they accounted for 31 (58%) of cases, whereas Bukowski et al. showed that they are usually involved in only 23.6% of IUFD.[4] Moreover, no genetic causes were observed while infectious and fetal causes were rarely found (one case of each), although Bukowski et al demonstrated that such etiologies are involved in respectively 29.3, 13.7 and 12.9% of IUFD. This reveals the selection bias which applied while referring the patients to our department: a thorough etiological assessment had previously been conducted by the obstetrician, thus ruling out the most common causes such as genetics, infections or fetal pathologies. Overall, 36/53 (68%) patients were referred to investigate IUFD due to inflammatory or vascular placental disorders, which demonstrates the obstetricians' expectations concerning internists in this field.

IUFD remains unexplained in 21% of cases which is comparable to the literature [4 10 11]. These include the 4 patients whose placenta was not examined. This emphasizes the crucial importance of performing placental pathological examinations.

In our study, as previously demonstrated, placental examination was highly contributive [12 13], since significant histological lesions were noted in 40/49 (81%) cases (including cord abnormalities in 4 cases).

As for patients with placental abnormalities, only 5/36 (14%) were found to have APS meeting Sydney criteria.[5] Unsurprisingly, history of thrombosis was significantly associated with the diagnosis of definite APS (p=0.001).[14] Among histological patterns, placental infarcts

were associated with APS (p=0.047), whereas other lesions such as fetal thrombosis or villitis were not: this is consistent with previous studies which showed that infarcts is the most common pathological feature encountered in patients with obstetrical APS.[15 16] These results emphasize the need for APL testing in patients presenting a VTE history or placental infarcts. Diagnosing obstetrical APS is essential since such patients may benefit from the association of aspirin and heparin, which increases the live birth rate for future pregnancies up to 70%.[17 18]

"Non-criteria" APS was discussed in 4/36 (11%) patients, because of intermittent LA positivity and low-titers aCL in one of them, and isolated anti-prothrombin positivity in the 3 others. In our study, "non-criteria" APS patients were not different from non-APS patients regarding clinical or pathological features. Notably, they showed neither a larger history of thrombosis, nor more placental infarcts. This finding does not support the relevance of an entity such as "non-criteria" APS. The best treatment regimen whose would benefit to patients with "non-criteria" APS for future pregnancies is still debated[19 20], although Mekinian et al recently showed that they may benefit from the same treatment as patients with definite definite APS.[21]

Above all, 27/36 (75%) patients did not have APS although they exhibited significant placental lesions. Placental inflammatory disorders, including villitis and intervillitis were found in 3 of our patients (8%). Their physiopathology remains unclear in most of cases[22]; nevertheless previous studies have shown that such lesions might not be associated to APS.[15 23-26]

The final question is to find out how to manage the future pregnancies of the 24/36 (67%) APL negative patients who presented an IUFD related to placental vascular disorders. Aspirin is often prescribed, sometimes associated to heparin by analogy with APS patients. Nevertheless, previous studies have failed to demonstrate the validity of such attitude so far.

[27-29] This situation raises the need for studies aiming at determining the best treatment options in non-APS patients presenting IUFD of placental vascular origin.

CONCLUSION

The investigation of IUFD requires close multi-disciplinary collaboration, in which the internist should play a substantial role. APL testing is a major feature of IUFD exploration, particularly in cases of maternal venous thromboembolism history or in cases of placental infarcts, as both were significantly associated to APS. Notably, most IUFD were found to originate from placental vascular disorders which were not related to APS: further studies are needed to determine the underlying mechanisms, in order to define the best treatment for future pregnancies.

Abbreviations used:

aCL : Anti Cardiolipin Antibodies

APL: Antiphospholipid antibodies

APS: Antiphospholipid Syndrome

β2-GPI: Anti β2 Glycoprotein I Antibodies

CNGOF : Collège National des Gynécologues-Obstétriciens Français/ French National College of Gynecologists and Obstetricians

IUFD: In Utero Feta Death

LA: Lupus Anticoagulant

LDA: Low-Dose Aspirin

LMWH: Low-Molecular-Weight Heparin

PE: Pre-Eclampsia

VTE: Venous Thrombo-Embolism

REFERENCES

1. Huchon C, Deffieux X, Beucher G *et al* (2016) Pregnancy loss: French clinical practice guidelines. Eur J Obstet Gynecol Reprod Biol 201:18–26

2. Alexander S, Zeitlin J (2016) Stillbirths and fetal deaths-Better definitions to monitor practice and policy across countries. BJOG Int J Obstet Gynaecol. doi: 10.1111/1471-0528.14381

3. Lawn JE, Blencowe H, Waiswa P *et al* (2016) Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet Lond Engl 387:587–603

4. Stillbirth Collaborative Research Network Writing Group (2011) Causes of death among stillbirths. JAMA 306:2459–2468

5. Miyakis S, Lockshin MD, Atsumi T *et al* (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost JTH 4:295–306

6. Rodríguez-García V, Ioannou Y, Fernández-Nebro A, Isenberg DA, Giles IP (2015) Examining the prevalence of non-criteria anti-phospholipid antibodies in patients with anti-phospholipid syndrome: a systematic review. Rheumatol Oxf Engl 54:2042–2050

7. Khamashta M, Taraborelli M, Sciascia S, Tincani A (2016) Antiphospholipid syndrome. Best Pract Res Clin Rheumatol 30:133–148

8. Khong TY, Mooney EE, Ariel I *et al* (2016) Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement. Arch Pathol Lab Med 140:698–713

9. Frøen JF, Pinar H, Flenady V *et al* (2009) Causes of death and associated conditions (Codac): a utilitarian approach to the classification of perinatal deaths. BMC Pregnancy Childbirth 9:22

10. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A (2005) Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ 331:1113–1117

11. Smith GCS, Fretts RC (2007) Stillbirth. Lancet Lond Engl 370:1715–1725

12. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AEP (2014) Systematic review of placental pathology reported in association with stillbirth. Placenta 35:552–562

13. Zanconato G, Piazzola E, Caloi E, Iacovella C, Ruffo R, Franchi M (2007) Clinicopathological evaluation of 59 cases of fetal death. Arch Gynecol Obstet 276:619–623

14. Reynaud Q, Lega J-C, Mismetti P *et al*. (2014) Risk of venous and arterial thrombosis according to type of antiphospholipid antibodies in adults without systemic lupus erythematosus: a systematic review and meta-analysis. Autoimmun Rev 13:595–608

15. Viall CA, Chamley LW (2015) Histopathology in the placentae of women with antiphospholipid antibodies: A systematic review of the literature. Autoimmun Rev 14:446–471

16. Stone S, Pijnenborg R, Vercruysse L *et al* (2006) The placental bed in pregnancies complicated by primary antiphospholipid syndrome. Placenta 27:457–467

17. Rai R, Cohen H, Dave M, Regan L (1997) Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ 314:253–257

18. Bouvier S, Cochery-Nouvellon E, Lavigne-Lissalde G *et al* (2014) Comparative incidence of pregnancy outcomes in treated obstetric antiphospholipid syndrome: the NOH-APS observational study. Blood 123:404–413

19. Arachchillage DRJ, Machin SJ, Mackie IJ, Cohen H (2015) Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. Thromb Haemost 113:13–19

20. Ramires de Jesús G, Levy RA, Porter TF, Branch DW (2015) Limited evidence for diagnosing and treating “non-criteria obstetric antiphospholipid syndrome.” Thromb Haemost 114:651–652

21. Mekinian A, Bourrienne M-C, Carbillon L *et al* (2016) Non-conventional antiphospholipid antibodies in patients with clinical obstetrical APS: Prevalence and treatment efficacy in pregnancies. Semin Arthritis Rheum 46:232–237

22. Derricott H, Jones RL, Greenwood SL, Batra G, Evans MJ, Heazell AEP (2016) Characterizing Villitis of Unknown Etiology and Inflammation in Stillbirth. Am J Pathol 186:952–961

23. Van Horn JT, Craven C, Ward K, Branch DW, Silver RM (2004) Histologic features of placentas and abortion specimens from women with antiphospholipid and antiphospholipid-like syndromes. Placenta 25:642–648

24. Magid MS, Kaplan C, Sammaritano LR, Peterson M, Druzin ML, Lockshin MD (1998) Placental pathology in systemic lupus erythematosus: a prospective study. Am J Obstet Gynecol 179:226–234

25. Ogishima D, Matsumoto T, Nakamura Y, Yoshida K, Kuwabara Y (2000) Placental pathology in systemic lupus erythematosus with antiphospholipid antibodies. Pathol Int 50:224–229

26. Boog G (2008) Chronic villitis of unknown etiology. Eur J Obstet Gynecol Reprod Biol 136:9–15

27. Kaandorp SP, Goddijn M, van der Post JAM *et al* (2010) Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med 362:1586–1596

28. Duffett L, Rodger M (2015) LMWH to prevent placenta-mediated pregnancy complications: an update. Br J Haematol 168:619–638

29. Clark P, Walker ID, Langhorne P *et al* (2010) SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood 115:4162–4167

Captions:

Figure 1. Repartition of cases according to gestationnal age.

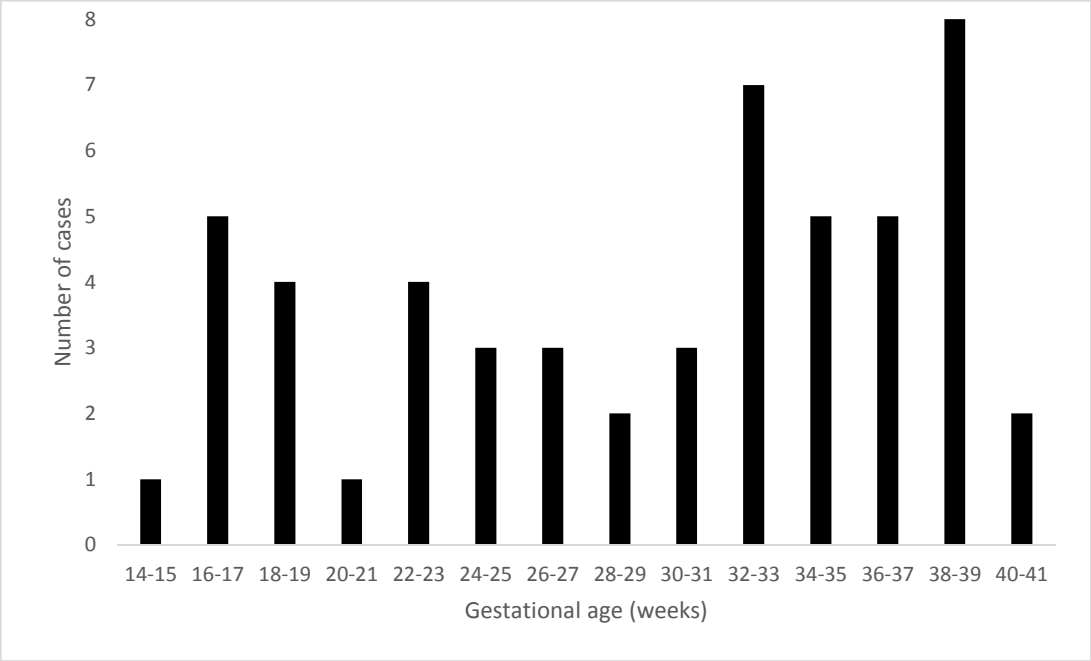

Figure 1. Distribution of cases according to gestationnal age.

Table 1. Main cause of In Utero Fetal Death, determined through expert agreement.

	Main cause of IUFD	N Total: 53	%
Abnormal placentas	Placental (27 PVD, 3 PID)	30	56.6
Abnormal placentas	Maternal disease (5 proven APS, 1 PE)	6	11.3
	Cord conditions	4	7.5
	Infection	1	1.9
	Fetal	1	1.9
	Intrapartum or obstetric complication	0	0
	Congenital/ genetic	0	0
	Unknown	11	20.8
	Total	53	100

Abbreviations: IUFD: In Utero Fetal Doss; PVD: Placental Vascular Disorders; PID: Placental inflammatory Disorders; APS: Antiphospholipid Syndrome; PE: Pre-Eclampsia.