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## Investigating in utero fetal death outcome of internal medicine consultation

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

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1 **Title page**

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

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18 **Running title:** Placenta related fetal death.

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

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## 26 ABSTRACT

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

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

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

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

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

1  
2  
3 50 **Keywords:** in utero fetal death, stillbirth, internal medicine, placental pathology,  
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5 51 antiphospholipid antibodies syndrome, placental vascular disorders  
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7 52 Tweetable abstract: a study analyzing the prevalence of fetal death related to placental  
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9 53 disorders in internal medicine.  
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## 15 55 **INTRODUCTION**

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18 56 There is currently no international consensus on the gestational age threshold which defines  
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20 57 In Utero Fetal Death (IUFD). The French National College of Gynecologists and  
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22 58 Obstetricians (CNGOF) defines IUFD as a spontaneous cessation of fetal cardiac activity  
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24 59 occurring before or during labor, after 14 weeks of amenorrhea <sup>1</sup>, whereas the threshold of  
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26 60 either 22 or 28 weeks or more is commonly used in many countries.<sup>2,3</sup>

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28 61 Bukowski et al <sup>4</sup> showed that obstetric complications, placental disease, genetic abnormality  
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30 62 and infections, were involved in respectively 29%, 26%, 13% and 13% of IUFD, then  
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32 63 followed by cord abnormalities (10.4%), hypertensive disorders (9.2%), and maternal  
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34 64 complications (7.8%). IUFD were considered idiopathic in 24% of cases.

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37 65 The objectives of IUFD investigations are to identify the cause, to prepare for future  
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39 66 pregnancies, and to detect a maternal pathology requiring specific care, such as  
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41 67 antiphospholipid antibodies syndrome (APS).<sup>1</sup>

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43 68 APS diagnosis requires the presence of clinical and biological criteria meeting the Sydney  
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45 69 classification criteria.<sup>5</sup> However, many patients, while fulfilling the clinical criteria, cannot be  
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47 70 classified as having APS either because of low titers or non-persistent positivity of  
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49 71 conventional antibodies, or because of the detection of other antibodies that have currently  
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51 72 not been validated (eg anti-prothrombin...): in those cases, the appellation of “non-criteria”  
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53 73 APS is sometimes used.<sup>6,7</sup>

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## 75 **Study objectives**

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

## 83 **METHODS**

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

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

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

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3 100 **Statistical methods**

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5 101 Categorical variables associations were analyzed by conducting a Chi square or Fisher exact  
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7 102 test. Quantitative data was analyzed by conducting student or Mann and Whitney U test. We  
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9 103 performed all tests with a significance level of  $P < 0.05$ . Statistical analysis was performed  
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11 104 using SPSS 20.0 software.

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13 105 This study was approved by the ethics committee of Rennes University Hospital.  
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19 107 **RESULTS**

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21 108 **Patients' characteristics**

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23 109 53 patients consulted in internal medicine for IUFD, all of whom were referred by their  
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25 110 obstetrician. 22 patients (42%) were primigravida, 5 patients (9%) had a history of IUFD, 9  
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27 111 patients (17%) had a history of miscarriage, 2 patients had an antecedent of preeclampsia, 2  
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29 112 patients an antecedent of HELLP syndrome. A history of severe fetal growth restriction (<5  
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31 113 percentile) was mentioned in two cases. One patient suffered from chronic hypertension, no  
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33 114 patients had diabetes mellitus and none had renal disease. 9 patients (13%) were overweight  
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35 115 or obese. Three patients were known to have APS, revealed in all cases by venous thrombo-  
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37 116 embolism (VTE). APS was considered as primary in all cases as none of our patient had  
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39 117 associated connective tissue disease. The patients' mean age at the time of IUFD was of 30  
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41 118 +/- 4.5 years (extremes: 19-42). The mean term was 29.2 weeks of amenorrhea +/- 7.9  
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43 119 (extremes 15-40). There were no multiple pregnancies. Distribution of IUFD according to  
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45 120 gestational age is shown in Figure 1.

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48 121 At the time of IUFD, 7/53 (13%) patients were receiving anticoagulant therapy or antiplatelet  
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50 122 agents: 4 patients were treated with low dose aspirin (LDA), because of previous fetal loss in  
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52 123 3 cases, and of severe fetal growth restriction in one case. The three patients with known  
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54 124 APS were receiving LDA combined with low-molecular-weight heparin (LMWH).  
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3 125 **Biology**

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5 126 Conventional APL (LA, aCL and  $\beta$ 2-GPI) were tested in 49/53 patients (90%), and were  
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7 127 positive in 9 (17%) cases.

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10 128 Among the 9 APL positive patients, 8 underwent repeat testing 12 weeks later. Among them,  
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12 129 5 still tested positive: they were classified as having definite APS. The four other patients  
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14 130 presented “non-criteria” APS: one of them was tested positive for LA without confirmation 12  
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16 131 weeks apart and presented low titers aCL, the 3 others were negative for conventional APL,  
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18 132 but tested positive for anti-prothrombin antibodies.

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20 133 **Pathological findings**

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22 134 A placental histological analysis was performed in 49/53 cases (92%). Anomalies were found  
23  
24 135 in 40/49 (81%) of the placentas.

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26 136 Vascular disorders were noted in 33/49 (73%) placentas. Retroplacental hematoma was  
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28 137 found in 10 cases, infarcts in 19 cases. Thrombosis were observed in 2 cases, decidual  
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30 138 arteriopathy was found in 3 cases. Fetal vascular malperfusion was observed in 7 patients,  
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32 139 only one of whom had gestational diabetes. Inflammatory disorders were found in 3 cases: 2  
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34 140 cases of villitis and one case of intervillitis, in all of which TORCH (Toxoplasmosis, Rubella,  
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36 141 CMV and Herpes virus) screening was negative. IUFD was related to cord anomaly in 4  
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38 142 cases: cord thrombosis in 3 cases, and tight loops in one case.

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41 143 All the placentas of the 9 APL positive patients (definite and “non-criteria” APS) were  
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43 144 examined: all presented vascular disorders, which associated hypotrophy (constant) with  
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45 145 decidual arteriopathy in one case, infarcts in 8/9 cases, retroplacental hematoma in 2 cases,  
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47 146 and thrombi in two cases. In one patient was noted the co-existence of fetal vascular  
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49 147 malperfusion.

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3 150 **Results of the consultation**

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5 151 The main causes of IUFD are reported in Table 1. Etiological categories were extracted from  
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7 152 the CODAC classification<sup>9</sup>: 6 cases issued from maternal causes, including the 5 definite  
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9 153 APS patients plus one patient whose IUFD was secondary to severe pre-eclampsia. IUFD of  
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11 154 “non-criteria” (n=4) and non-APS patients (n=27) were ruled as having a placental cause.  
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13 155 IUFD resulted from placental disorders in 36/53 (68%) patients: placental insufficiency in 33  
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15 156 (62%) cases (including one case of pre-eclampsia), and placental inflammatory disorders in 3  
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17 157 (6%) cases (Table 1). None of our patients had isolated gestational hypertension, renal  
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19 158 disease or connective tissue disease.  
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21 159 IUFD was caused by fetal anemia in one case which was classified as a fetal cause, by  
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23 160 Parvovirus B19 infection in one case, and by funicular pathology in 4 cases.  
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25 161 IUFD remained unexplained in 11/53 (21%) cases, including all the patients whose placenta  
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27 162 was not examined.  
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33 164 **Comparison between APS, “non-criteria” APS and non-APS patients**

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35 165 The 36 patients who had significant placental disorders were allocated to one of the following  
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37 166 groups according to their APS status: definite APS, “non-criteria” APS and non-APS (in which  
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39 167 the patient with pre-eclampsia was included as her placenta exhibited hypotrophia along with  
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41 168 massive infarct and retroplacental hematoma).  
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43 169 Only the three patients with known APS had VTE history. Comparisons between the three  
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45 170 groups revealed that antecedent of VTE (p=0.001) and placental infarcts (p=0.047) were  
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47 171 significantly associated with the definite APS group, whereas fetal vascular malperfusion or  
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49 172 inflammatory disorders (villitis/ intervillitis) were not. Patients with “non-criteria” APS were not  
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51 173 different from non-APS patients regarding VTE history or pathological findings.  
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3 174 There were no differences in mothers' age, time of pregnancy termination, presence of  
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5 175 livedo, history of fetal loss, or placental hypotrophia, between the 3 groups.  
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## 10 177 **DISCUSSION**

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12 178 53 cases of IUFD were referred to an internist over the study period. In the meantime, 440  
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14 179 cases were registered in our center, meaning that internists were consulted in 12% of cases.  
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16 180 Placental disorders were over represented, as they accounted for 31 (58%) of cases,  
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18 181 whereas Bukowski et al. showed that they are usually involved in only 23.6% of IUFD.<sup>4</sup>  
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20 182 Moreover, no genetic causes were observed while infectious and fetal causes were rarely  
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22 183 found (one case of each), although Bukowski et al demonstrated that such etiologies are  
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24 184 involved in respectively 29.3, 13.7 and 12.9% of IUFD. This reveals the selection bias which  
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26 185 applied while referring the patients to our department: a thorough etiological assessment had  
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28 186 previously been conducted by the obstetrician, thus ruling out the most common causes such  
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30 187 as genetics, infections or fetal pathologies. Overall, 36/53 (68%) patients were referred to  
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32 188 investigate IUFD due to inflammatory or vascular placental disorders, which demonstrates  
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34 189 the obstetricians' expectations concerning internists in this field.  
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37 190 IUFD remains unexplained in 21% of cases which is comparable to the literature<sup>4 10 11</sup>. These  
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39 191 include the 4 patients whose placenta was not examined. This emphasizes the crucial  
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41 192 importance of performing placental pathological examinations.  
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44 193 In our study, as previously demonstrated, placental examination was highly contributive<sup>12 13</sup>,  
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46 194 since significant histological lesions were noted in 40/49 (81%) cases (including cord  
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48 195 abnormalities in 4 cases).  
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50 196 As for patients with placental abnormalities, only 5/36 (14%) were found to have APS  
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52 197 meeting Sydney criteria.<sup>5</sup> Unsurprisingly, history of thrombosis was significantly associated  
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54 198 with the diagnosis of definite APS ( $p=0.001$ ).<sup>14</sup> Among histological patterns, placental infarcts  
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199 were associated with APS ( $p=0.047$ ), whereas other lesions such as fetal thrombosis or  
200 villitis were not: this is consistent with previous studies which showed that infarcts is the most  
201 common pathological feature encountered in patients with obstetrical APS.<sup>15 16</sup> These results  
202 emphasize the need for APL testing in patients presenting a VTE history or placental infarcts.  
203 Diagnosing obstetrical APS is essential since such patients may benefit from the association  
204 of aspirin and heparin, which increases the live birth rate for future pregnancies up to 70%.<sup>17</sup>

205<sup>18</sup>  
206 “Non-criteria” APS was discussed in 4/36 (11%) patients, because of intermittent LA  
207 positivity and low-titers aCL in one of them, and isolated anti-prothrombin positivity in the 3  
208 others. In our study, “non-criteria” APS patients were not different from non-APS patients  
209 regarding clinical or pathological features. Notably, they showed neither a larger history of  
210 thrombosis, nor more placental infarcts. This finding does not support the relevance of an  
211 entity such as “non-criteria” APS. The best treatment regimen whose would benefit to  
212 patients with “non-criteria” APS for future pregnancies is still debated<sup>19 20</sup>, although Mekinian  
213 et al recently showed that they may benefit from the same treatment as patients with definite  
214 definite APS.<sup>21</sup>

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

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

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3 224 <sup>27-29</sup> This situation raises the need for studies aiming at determining the best treatment  
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5 225 options in non-APS patients presenting IUFD of placental vascular origin.  
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10 227 **CONCLUSION**

11  
12 228 The investigation of IUFD requires close multi-disciplinary collaboration, in which the internist  
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14 229 should play a substantial role. APL testing is a major feature of IUFD exploration, particularly  
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16 230 in cases of maternal venous thromboembolism history or in cases of placental infarcts, as  
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18 231 both were significantly associated to APS. Notably, most IUFD were found to originate from  
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20 232 placental vascular disorders which were not related to APS: further studies are needed to  
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22 233 determine the underlying mechanisms, in order to define the best treatment for future  
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24 234 pregnancies.  
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30 236 **Abbreviations used:**

31  
32 237 **aCL** : Anti Cardiolipin Antibodies

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34 238 **APL**: Antiphospholipid antibodies

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36 239 **APS**: Antiphospholipid Syndrome

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38 240 **β2-GPI**: Anti β2 Glycoprotein I Antibodies

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40 241 **CNGOF** : Collège National des Gynécologues-Obstétriciens Français/ French National

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42 242 College of Gynecologists and Obstetricians

43  
44 243 **IUFD**: In Utero Feta Death

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46 244 **LA**: Lupus Anticoagulant

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48 245 **LDA**: Low-Dose Aspirin

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50 246 **LMWH**: Low-Molecular-Weight Heparin

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52 247 **PE**: Pre-Eclampsia  
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248 **VTE:** Venous Thrombo-Embolism

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For Peer Review Only

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328 **Captions:**

329 Figure 1. Repartition of cases according to gestationnal age.

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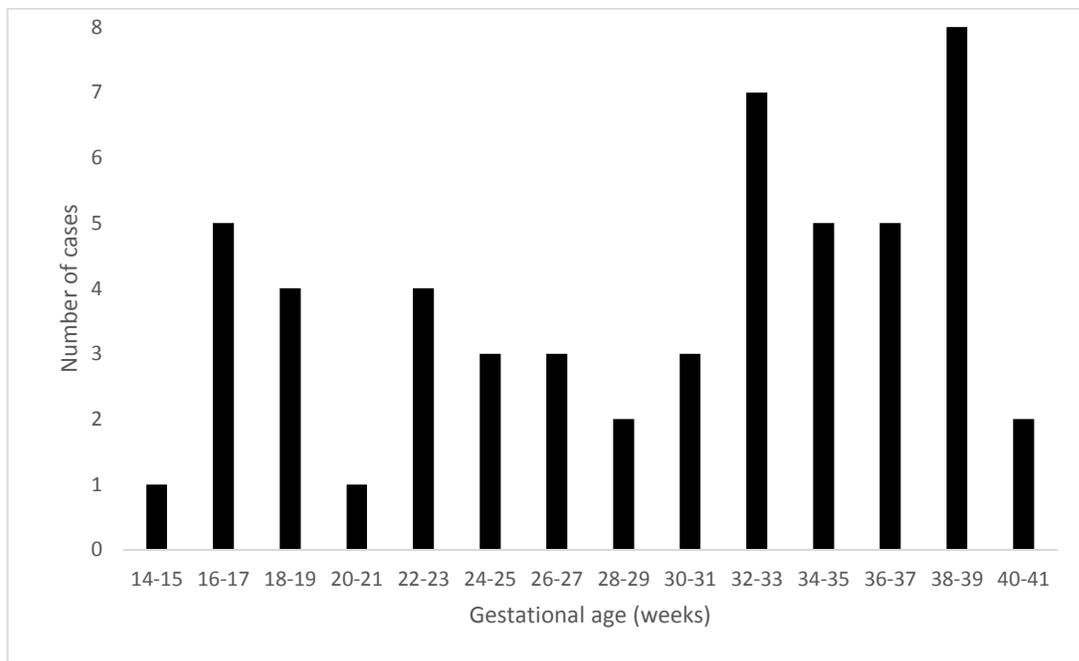


Figure 1. Distribution of cases according to gestational age.

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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
	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 Death; PVD: Placental Vascular Disorders; PID: Placental inflammatory Disorders; APS: Antiphospholipid Syndrome; PE: Pre-Eclampsia.