Placental vascular pathology and increased thrombin generation as mechanisms of disease in obstetrical syndromes

Obstetrical complications including preeclampsia, fetal growth restriction, preterm labor, preterm prelabor rupture of membranes and fetal demise are all the clinical endpoint of several underlying mechanisms (i.e. infection inflammation, thrombosis, endocrine disorder, immunologic rejection, genetic, and environmental), therefore, they may be regarded as syndromes. Placental vascular pathology and increased thrombin generation were reported in all of these obstetrical syndromes. Moreover, elevated concentrations of thrombin-anti-thrombin III complexes and changes in the coagulation as well as anticoagulation factors can be detected in the maternal circulation prior to the clinical development of the disease in some of these syndromes. In this review, we will assess the changes in the hemostatic system during normal and complicated pregnancy in maternal blood, maternal-fetal interface and amniotic fluid, and describe the contribution of thrombosis and vascular pathology to the development of the great obstetrical syndromes.

1 **Placental Vascular Pathology and Increased Thrombin Generation as Mechanisms of**

2 **Disease In Obstetrical Syndromes**

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20 **1.   Introduction**

21 Obstetrical complications including preeclampsia, fetal growth restriction, preterm labor, preterm

22 prelabor rupture of membranes and fetal demise are all the clinical endpoint of several underlying

23 mechanisms (i.e. infection inflammation, thrombosis, endocrine disorder, immunologic rejection,

24 genetic, and environmental), therefore, they may be regarded as syndromes. In this review, we

25 will assess the changes in the hemostatic system during normal and complicated pregnancy in

26 maternal blood, maternal-fetal interface and amniotic fluid, and describe the contribution of

27 thrombosis and vascular pathology to the development of the great obstetrical syndromes.

28 **2. What are the great obstetrical syndromes?**

29   The major obstetrical complications including preeclampsia, intrauterine growth restriction

30   (IUGR), preterm labor (PTL), preterm prelabor rupture of membranes (PROM), fetal demise, and

31   recurrent abortions are all syndromes, also defined as "great obstetrical syndromes". As reported

32   in The Oxford Medical Dictionary a syndrome is 'a combination of symptoms and/or signs that

33   form a distinct clinical picture indicative of a particular disorder'. Hence, they represent the

34   clinical manifestation of many possible underlying mechanisms of disease[1].

35   Key features of these syndromes are[2]: multiple etiologies; long preclinical stage; frequent fetal

36   involvement; clinical manifestations which are often adaptive in nature; and predisposition to a

37   particular syndrome is influenced by gene–environment interaction and/or complex gene-gene

38   interactions involving maternal and/or fetal genotypes. These mechanisms of disease were

39   identified and reported in all the obstetrical complications listed above. This review is focused on

40   the role of thrombosis and vascular pathology of the placenta in these syndromes.

41   **3. What are the changes in the coagulation system during normal pregnancy?**

42   In term of the coagulation and hemostatic systems there are several major compartments: the

43   maternal circulation, the fetal maternal interface (the placenta, and membranes), amniotic fluid

44   and the fetus that each has a specific behavior during gestation. The changes in the coagulation

45   system during gestation are considered to be adaptive mechanisms and are aimed to: 1) the

46   prevention of bleeding at the time of trophoblast implantation and the delivery of the fetus; 2)

47   allow the laminar flow and the intervillous space; and 3) seal amniotic fluid leak and reduce

48   obstetrical bleeding[3-7]. Of interest, the fetus is somewhat less involved and its coagulation system

49   develops during gestation, and this subject is beyond the scope of this review.

50   Indeed, normal pregnancy has been associated with excessive maternal thrombin generation[3, 8]

51   and a tendency for platelets to aggregate in response to agonists[9, 10]. Pregnancy is accompanied by

52   2 to 3-fold increase in fibrinogen concentrations and 20% to 1000% increase in factors VII, VIII,

53   IX, X, and XII, all of which peak at term[11]. The concentrations of vWF increase up to 400% by

54   term[11]. By contrast, those of pro-thrombin and factor V remain unchanged while the

55   concentrations of factors XIII and XI decline modestly[12]. Indeed there is evidence of chronic low-

56   level thrombin and fibrin generation throughout normal pregnancy as indicated by enhanced

57   concentrations of pro-thrombin fragment 1.2, thrombin-antithrombin (TAT) III complexes, and

58   soluble fibrin polymers[13]. Free protein S concentration declines significantly (up to 55%) during

59   pregnancy due to increased circulating complement 4B-binding protein its molecular carrier.

60   Protein S nadir at delivery and this reduction is exacerbated by cesarean delivery and infection[11,

61   12]. As a consequence, pregnancy is associated with an increase in resistance to activated protein

62 C[12, 13]. The concentrations of PAI-1 increase by 3 to 4-folds during pregnancy while plasma PAI-2

63 values, which are negligible before pregnancy reach concentrations of 160 mg/L at delivery[11].

64 Thus, pregnancy is associated with increased clotting potential, as well as decreased

65 anticoagulant properties, and fibrinolysis[14]. Therefore, it can be defined as a prothrombotic state.

66 One of the most important mediators of the hypercoagulable state of normal pregnancy is tissue

67 factor (TF). Indeed, there is a substantial increase in TF concentrations in the decidua and

68 myometrium[15-18], preventing placental abruption since this leads to an increase in the efficiency of

69 clotting function[14]. The placenta is a source of TF, since trophoblast cells constitutively express it,

70 behaving as activated endothelium, and leading to a condition of procoagulant state that, if not

71 controlled by anticoagulant mechanisms, predisposes to thrombotic complications[15]. The

72 principal anticoagulant mechanism inhibiting TF activation pathway is tissue factor pathway

73 inhibitor (TFPI), which mRNA is highly expressed in the macrophages in the villi in term

74 placenta[19].

75 Similarly, high TF concentrations have been detected in the fetal membranes (mainly the amnion)

76 and amniotic fluid[7, 20-23]. TFPI has been found in amniotic fluid as well[20], but it is not clear if the

77 presence of TF and its natural inhibitor is related to coagulation per se or is somehow connected

78 with embryonic development[24].

79 In contrast to the changes detected in the amniotic fluid and the decidua, the median maternal

80 plasma immunoreactive TF concentration of normal pregnant women do not differ significantly

81 from that of non-pregnant patients[3, 25]. However, labor at term increases significantly the maternal

82 plasma immunoreactive TF concentration in comparison to the non-pregnant state[20]. In addition

83 to the changes in TF, normal pregnancy is associated with increased thrombin generation[3, 8], as

84 determined by the elevation of maternal concentrations of fibrinopeptide A, prothrombin

85 fragments (PF) 1 and 2, and thrombin–antithrombin (TAT) III complexes[7, 26-28]. The concentration

86 of these complexes further increases during and after normal parturition[27, 29], and subsequently

87 decreases during the puerperium[27, 29].

88 **4. What are the changes in the hemostatic system associated with the great obstetrical**

89 **syndromes?**

90 The great obstetrical syndromes are associated with changes in the hemostatic and vascular

91 systems in the compartments mentioned above: 1) the maternal circulation; 2) the feto-maternal

92 interface of placenta and membranes; 3) and the amniotic fluid.

93 **4.1 Changes in the hemostatic system of women with obstetrical syndromes.**

94   The involvement of the hemostatic system in the pathophysiology of these obstetrical syndromes

95   is becoming more and more apparent. Indeed, increased thrombin generation is reported in the

96   maternal circulation of women with preeclampsia[30-34], IUGR[30-32, 35, 36], fetal demise[37], PTL[8, 37, 38] and

97   preterm PROM[8, 37, 39].

98   There are several possible explanations for the increased thrombin generation in these patients: 1)

99   increased activation of coagulation cascade in the maternal circulation due to pathological

100 processes including bleeding or inflammation; and 2) depletion of anticoagulation proteins that

101 subsequently leads to increased thrombin generation (Table 1).

4.1.1 Increased activation of the coagulation cascade and thrombin generation in the maternal circulation in patients with pregnancy complications

104 All the obstetrical syndromes including preeclampsia[30-34, 40, 41], IUGR[31, 32, 35, 36], fetal demise[37], PTL[8,

105 38] and preterm PROM[8, 37, 39] are associated with a higher maternal thrombin generation than a

106 normal pregnancy. These may be of clinical implication since in women with preterm labor,

107 elevated maternal plasma TAT III complexes concentration was associated with a higher chance

108 to deliver within <7 days from admission[37] (Fig. 1). To further understand how does thrombin

109 affect the duration of pregnancy and the clinical phenotype of patients with the obstetrical

110 syndromes we need to consider what are the mechanisms leading to thrombin generation and how

111 it affects the feto-maternal unit.

112 Increased thrombin generation can result from the following underlying mechanisms: 1) decidual

113 hemorrhage that leads to a retro-placental clot formation[42]; 2) intra-amniotic

114 infection/inflammation which can induce decidual bleeding and sub-clinical abruption[43] , as well

115 as increased intra-amniotic TAT complexes[37]; and 3) an increased maternal systemic

116 inflammatory response[44] that may activate the extrinsic pathway of coagulation due to the

117 expression and release of TF by activated monocytes[45].

118 Thrombin affects many systems including also the following: 1) stimulation of decidual cell

119 secretion of matrix metalloproteinase (MMP) (i.e. MMP-1 and MMP-3) that can degrade the

120 extracellular matrix of the chorioamniotic membranes[46, 47] (as in preterm PROM); 2) myometrial

121 activation and uterine contractions generation that may lead to preterm labor with or without

122 rupture of membranes and a subsequent preterm delivery[38, 48, 49]; and 3) thrombin has an inhibitory

123 effect on the production of TFPI by endothelial cells[50], and the increased thrombin generation

124 observed in patients with PTL may be associated with a concomitant reduction in TFPI

125 production by the maternal vascular endothelium (the depletion of anticoagulant proteins will be

126 discussed in the following section of this review).

127   There is evidence to support that the extrinsic pathway of coagulation is activated in many of

128   these pregnancy complications and it is the source of the increased thrombin generation[51]. Indeed,

129   increased immunoreactive TF concentrations were reported in women with preeclampsia and

130   those with preterm PROM[52]. Moreover, the contribution of preeclampsia to elevated maternal

131   immunoreactive TF persisted also among patients with fetal demise, while those with fetal death

132   who were normotensive did not have higher median TF concentration than normal pregnant

133   women. Moreover, the median TF concentration of patients with preeclampsia was also higher

134   than in patients with fetal demise without hypertension. These findings are consistent with

135   previous studies[3, 53], suggesting that elevated TF immunoreactivity and activity may be associated

136   with the pathophysiologic process leading to preeclampsia, rather than being a consequence of

137   the fetal death.

138   In some of the obstetrical syndromes there was elevated TF activity in the maternal circulation

139   without a concomitant increase in the plasma concentration of this factor. This was the case

140   among patients with a small for gestational age (SGA) neonate and those with preterm labor [31, 54]

141   (Table 1). This suggests that the increased TF activity among patients with PTL as well as those

142   with an SGA neonate, contributes to a higher generation of factor Xa that, along with the

143   physiologic increase in the maternal plasma concentrations of factor VII and factor X during

144   gestation[11, 55-57], may be the underlying mechanism leading to the increased thrombin generation

145   reported these syndromes.

146   The differences between PTL and preterm PROM in term of maternal plasma TF concentration

147   and activity may derive from the specific component of the common pathway of parturition,

148   which is activated in each obstetrical syndrome[58]. While preterm PROM is associated with the

149   activation of the decidua and the membranes, myometrial activation is the major component of

150   preterm labor with intact membranes[58]. This is relevant because the decidua and the membranes

151   have a high TF concentration[17, 18, 59].

152   In summary, the evidence brought herein suggests that increased thrombin generation in patients

153   with the great obstetrical syndromes may reflect the activation of the coagulation cascade mainly

154   through the extrinsic arm. This activation can be attributed to various underlying mechanisms.

155   **4.1.2 Depleted or insufficient anticoagulant proteins concentration**

156   In the normal state there is a delicate balance between the proteins activating/participating the

157   coagulation cascade and their inhibitors. Increased thrombin generation may result, as we

158   presented above, from activation of the coagulation cascade due to higher concentrations or

159   activities of the proteins included in the coagulation cascade. However, thrombin generation can

160   also result from insufficient concentration or activity of anticoagulation proteins.

161   Tissue factor pathway inhibitor (TFPI), a glycoprotein comprising of three Kunitz domain[60] that

162   are specific inhibitors of trypsin-like proteinases[61], is the main inhibitor of the extrinsic pathway

163   of coagulation. TFPI inhibits thrombin generation through the inactivation of activated factor X

164   and the factor VIIa/TF complex[60, 62]. The mean maternal plasma concentrations of total TFPI

165   increases during the first half of pregnancy, remains relatively constant in the second half[63] and

166   decreases during labor[20]. There are two types of TFPI: 1) TFPI-1 is the more prevalent form in

167   the non-pregnant state in the maternal circulation and can also be found in the fetal blood,

168   platelets, endothelial cells and other organs[19, 64]; and 2) TFPI-2- the major form of TFPI in the

169   placenta[65-68], also known as Placental Protein 5 (PP5)[69, 70]. During pregnancy, the maternal plasma

170   concentration of TFPI-2 increases gradually, reaches a plateau at 36 weeks and subsides after

171   delivery[71-74].

172   The overall balance between the concentration and activity of the coagulation factors and the

173   anti-coagulation proteins is one of the determining factors of thrombin generation. In the normal

174   state, the immunoreactive concentrations of TFPI in the plasma are 500 to 1000 times higher than

175   that of TF[75], suggesting that an excess of anti-coagulant proteins closely controls the coagulation

176   cascade activity. The median maternal plasma TFPI concentration increases during

177   preeclampsia[53, 76], which is associated with an exaggerated maternal systemic inflammatory

178   response. However, the increase in the median maternal TF plasma concentration is such that the

179   overall balance between TF and its inhibitor is affected leading to increased thrombin generation

180   in this syndrome. In contrast to preeclampsia, maternal plasma TFPI concentration decreases in

181   patients with PTL[52] and preterm PROM[77] regardless to the presence of intra-amniotic

182   infection/inflammation, as well as in women with fetal demise[54], and does not change in mothers

183   with SGA fetuses[53]. Overall these findings suggest that the increased thrombin generation

184   observed among these patients may derive not only from an increased activation of the

185   hemostatic system, but also from insufficient anti-coagulation, as reflected by the lower TFPI

186   concentrations (Fig. 2).

187   A possible explanation of the lower maternal plasma concentration observed in some of the

188   obstetrical syndromes may be that during these syndromes there is a reduction in the placental

189   production of TFPI[65, 66, 69, 76] (mainly TFPI-2), contributing to the low maternal plasma

190   concentrations detected in patients with PTL, in addition to the thrombin inhibitory effect to TFPI

191   expression on endothelial cells, as above mentioned. Indeed, patients with vascular complications

192   of pregnancy (preeclampsia, eclampsia, placental abruption, fetal growth restriction, and fetal

193   demise) have a lower placental concentration of total TFPI, and TFPI mRNA expression than in

194   women with normal pregnancies[78, 79].

195   Other proteins implicated in the inhibitory control of the coagulation cascade are protein S,

196   protein C and protein Z. Protein S is a cofactor to protein C in the inactivation of factors

197   Va and VIIIa. This protein exists in two forms: a free form and a complex form bound

198   to complement protein C4b-binding protein (C4BP). Only the free form is active[80]. Protein S also

199   acts as a TFPI cofactor, in the presence of weak pro-coagulant stimuli, by enhancing the

200   interaction of TFPI with factor Xa while using Ca2+ and phospholipids in the process[81] without

201   increasing inhibition of factor VIIa-TF by TFPI[82]. During pregnancy there is a physiologic

202   change in the relationship between the bound and the free forms of protein S in the maternal

203   plasma. The increase in C4BP during gestation reduces free protein S concentration in up to 55%

204   of its value out of pregnant state, reaching its nadir at delivery. Of interest, cesarean delivery and

205   infection exacerbate the reduction in free protein S concentrations[11, 83]. Moreover, a functional

206   protein S deficiency can explain a poor response to activated protein C[84].

207   The association between the alteration of concentration and function of protein S and protein C in

208   the great obstetrical syndromes is not completely clear. The evidence regarding the association of

209   protein S and protein C deficiency and preeclampsia is controversial[85, 86].

210   While some reported an association between protein S deficiency and an increased risk for this

211   syndrome (especially for early onset preeclampsia)[85] others could not demonstrate this effect[86].

212   There is some evidence regarding the relation of protein S deficiency and increased risk of

213   stillbirth[87] and mid-trimester IUGR[88]. An increased risk of stillbirth has been reported in patients

214   with protein S deficiency while the risk was not significantly increased in cases of protein C

215   deficiency[87], and Kupferminc et al[88] found that protein S, but not protein C deficiency, was

216   significantly associated with severe mid-trimester IUGR.

217   Protein Z, in complex with protein Z-dependent protease inhibitor (ZPI) (Fig. 3)[89-91], acts as a

218   physiologic inhibitor of activation of prothrombin by factor Xa. Protein Z is a vitamin

219   K-dependent plasma glycoprotein[92] that is an essential cofactor for ZPI activity. In the absence of

220   protein Z, the activity of ZPI is reduced by more than 1000-fold[91]. Normal pregnancy is

221   characterized by an increased plasma concentration of protein Z[93], probably as a compensation

222   for the increase of factor X concentration. Women with preterm labor without intra-amniotic

223   infection or inflammation and those with vaginal bleeding who delivered preterm had a lower

224   median maternal plasma protein Z concentration than women with a normal pregnancy and those

225   with vaginal bleeding who delivered at term[94]. The changes of protein Z concentrations in other

226   pregnancy complications are controversial. Some demonstrated that the median plasma

227 concentration of protein Z in patients with preeclampsia, IUGR, and late fetal death were not

228 significantly different than that of patients with a normal pregnancy[95]. Others reported lower

229 median maternal plasma protein Z concentrations in women with preeclampsia or pyelonephritis

230 and higher proportion of protein Z deficiency (defined as protein Z plasma concentration below

231 the 5th percentile) in patients with preeclampsia or fetal demise than in those with a normal

232 pregnancy[96]. Moreover, increased maternal plasma anti-protein Z antibodies concentrations were

233 associated with SGA neonates, fetal demise and preeclampsia.

234 The information presented above suggest that it is not only the concentration of one coagulation

235 factor or anticoagulation protein, but rather the overall balance between the coagulation factors

236 and their inhibitors that increases thrombin generation in the great obstetrical syndromes. Indeed,

237 although preterm labor was not associated with a significant change in the median maternal

238 plasma TF concentration, the TFPI/TF ratio of these patients was lower than that of normal

239 pregnant women, mainly due to decreased TFPI concentrations.

240 This observation was also reported in patients with preterm PROM[77], and those with

241 preeclampsia[53]. The lower TFPI/TF ratio in patients with preeclampsia occurs despite the increase

242 in the median maternal plasma TFPI concentration observed in these patients. This suggests that

243 the balance between TF and its natural inhibitor may better reflect the overall activity of the TF

244 pathway of coagulation, than the individual concentrations of TF or TFPI.

245 Collectively, these observations suggest that our attention should be focused not only on the

246 coagulation protein but also on their inhibitors since an imbalance between them may contribute

247 to increased thrombin generation leading to the onset of the great obstetrical syndromes.

4.2 Changes in the feto-maternal interface

248
249 Normal placental development and the establishment of an adequate feto-maternal circulation are
250 key points for a successful pregnancy. The networks of the placental vascular tree either on the
251 maternal or fetal side are dynamic structures that can be substantially altered in cases of abnormal
252 placentation and trophoblast invasion. The human trophoblast has properties of endothelial cells
253 and can regulate the degree of activation of the coagulation cascade in the intervillous space[97, 98].
254 The villous trophoblasts express heparin sulfate, protein C and protein Z on their surface that
255 serve as anticoagulant that sustain laminar blood flow through the intervillous space. On the other
256 hand, unlike the endothelium of other organs, the trophoblast constantly presents the active
257 placental isoform of TF on its surface[98-101]. This isoform has a higher affinity for factor VIIa[102] ,
258 which may lead to increased activation of the coagulation cascade. One of the leading
259 pathological processes observed in all these syndromes is thrombosis and vascular abnormality of
260 the placenta at the maternal-fetal interface. The incidence of these pathological processes varies
261 among the different syndromes being more prevalent in preeclampsia, IUGR, and fetal demise
262 than in PTL and preterm PROM[30, 31, 37, 38].

4.2.1 Placental pathology in the Great Obstetrical Syndromes

263
264 There is a range of placental vascular and thrombotic lesions that are being observed in placentas
265 of patients with pregnancy complications. Thrombotic events of placental vessels can cause an
266 impairment of placental perfusion, leading to fetal growth restriction (FGR), preeclampsia and
267 fetal death as well as in some extents to PTL and preterm PROM[103, 104]. The frequency of the
268 specific vascular placental lesions varies among these obstetrical syndromes[105].
269 Placental vascular lesions are divided into maternal or fetal vascular origin (figure 4-5)[106, 107].
270 Lesions of the maternal vascular compartment include placental marginal and retro-placental
271 hemorrhages, lesions related to maternal under perfusion (acute atherosis and mural hypertrophy,
272 increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, villous
273 infarcts)[106]. Placental fetal vascular obstructive lesions are the result of stasis, hypercoagulability
274 and vascular damage within the fetal circulation of the placenta. Placental fetal vascular
275 abnormalities include: cord-related abnormalities (as torsion of cord, over-coiling, strictures and
276 tight knots[108]) and vascular lesions consistent with fetal thrombo-occlusive disease (thrombosis of
277 the chorionic plate and stem villous vessels, fibrotic, hypo-vascular and avascular villi[106]. In
278 addition, villitis of unknown etiology or chronic villitis, defined as lymphohistiocytic

279   inflammation localized to the stroma of terminal villi but often extending to the small vessels of

280   upstream villi is also associated with obliterative fetal vasculopathy[106] (Fig. 4-5).

281   **Preeclampsia:** The classical example for an association between obstetrical syndrome and

282   vascular placental lesions is preeclampsia. Women who develop preeclampsia have an increased

283   rate of abnormalities of the maternal side of the placental circulation and maternal

284   underperfusion[109, 110]. The frequency of these lesions is inversely related to the gestational age in

285   which the hypertensive disorder was diagnosed. The earliest the development of

286   hypertension/preeclampsia the more severe are the vascular lesions[111, 112]. Moreover, Kovo et al[113]

287   reported that the presence of fetal growth restriction in women with preeclampsia increases also

288   the frequency of fetal vascular lesions. Indeed, patients with early-onset preeclampsia

289   complicated by FGR had a higher rate of fetal-vascular supply lesions consistent with fetal

290   thrombo-occlusive disease than women with early-onset disease without FGR[113].

291   An assessment of the pathologic changes in placental hemostatic system has been performed in

292   patients with preeclampsia. Teng et al[114] studied TF and TFPI placental levels in pregnant patients

293   with preeclampsia, compared to normal pregnancies. They found increased TF placental

294   expression and a reduced expression of TFPI-1 and TFPI-2, with a significant correlation

295   between the levels of TF and TFPI-2 between maternal plasma and placenta.

296   **Fetal growth restriction:** Placentas from pregnancies complicated by FGR are smaller and have

297   significantly increased maternal and fetal vascular lesions compared to placentas from normal

298   pregnancies with   appropriate for gestational age neonates (AGA)[115, 116]. Maternal vascular

299   lesions were detected in about 50% of placentas from pregnancies complicated with FGR at term,

300   compared to only 20% in normal pregnancies, while fetal vascular lesions were observed in 11%

301   of FGR pregnancies compared to only 4% in placentas from normal pregnancies[113].

302   Placentas from normotensive pregnancies complicated by early-onset FGR (<34 weeks of

303   gestation) had a higher rate of low placental weight (<10th percentile) and maternal

304   underperfusion, as compared to placentas of women who delivered AGA neonates ≤34 weeks of

305   gestation[115]. Of interest, placentas from the late onset FGR group (after 34 weeks of gestation), in

306   addition to the high maternal vascular abnormalities, show also more fetal vascular abnormalities,

307   compared with AGA controls who delivered >34 weeks[117].

308   **Fetal demise:** Placental disease has been recognized as an important contributor to unexplained

309   fetal demise. Fetal vascular abnormalities[105] are extensively involved in early and late fetal death

310   rather than maternal vascular lesions. In fetal death occurring prior to 34 weeks, an earlier and

311 extended insult in the placental development occurs. On the other hand, late fetal demise is an
312 unpredicted event that is mostly characterized by non-thrombotic cord related lesions and less
313 placental vascular compromise[107].

314 **Preterm labor and preterm PROM:** Placental studies in PTL demonstrated a combination of
315 inflammatory and vascular lesions. PTL is generally attributed to an inflammatory response
316 involving the bacterial induction of cytokine and prostanoid production[118]. Finding of histological
317 chorioamnionitis in PTL[119] has established infection and inflammation as a causative factor of
318 preterm birth, moreover, noninfectious trigger may also contribute to the development of preterm
319 labor and in some instances may be evident by placental sterile inflammatory response[120] . In
320 addition, isolated placental vascular lesions, mostly of maternal supply, were reported in 20% of
321 cases of PTL and an additional 20% had combined inflammatory and vascular lesions. Moreover,
322 there are consistent reports describing increased rate of failure of transformation of the spiral
323 arteries in women with preterm labor without intrauterine infection/inflammation and in those
324 with preterm PROM than in women with normal pregnancies[121]. Such findings imply that an
325 inadequate uteroplacental blood flow due to abnormal placentation plays an important role in
326 pathogenesis of preterm parturition[121, 122].

328 Collectively, placental vascular lesions were reported in all the great obstetrical syndromes. The
329 severity of these lesions is associated with the timing of diagnosis of the disease. The more severe
330 the vascular injury, the more likely these complications will become clinically evident prior to 34
331 weeks of gestation. Of interest, vascular lesions often come along with evidence of acute
332 inflammation or lesions associated with chronic inflammatory processes, suggesting that
333 sometimes more than one mechanism is involved in development of a specific obstetrical
334 syndrome.

335 **4.3. Hemostatic changes in the amniotic fluid of women with obstetrical syndromes**
336 During normal pregnancy, there is an increase in the amniotic fluid TF concentration [7, 20-23]. In
337 order to demonstrate the association of hemostatic changes and the development of obstetrical
338 complications, Erez et al[54] studied the changes in the intra-amniotic concentration of TAT III
339 complexes, as well as TF concentration and activity, in cases of fetal demise and in normal
340 pregnancies.
341 Patients with a fetal demise had higher median amniotic fluid–TF concentration and activity than
342 those with normal pregnancies. Moreover, among patients with a FD there was a significant
343 correlation (Fig. 6) between the amniotic fluid–TF concentrations and activity (r =0.88, P

344 <0.0001). The median amniotic fluid– TAT III complexes concentration did not differ

345 significantly between the groups (normal pregnancy: median: 66.3 mg/l, range 11.4–2265.4 vs.

346 FD: median: 59.3 mg/l, range: 13.6–15,425.3; P =0.7). In their study, the median amniotic fluid–

347 TF concentration in normal pregnant women was 10 fold higher than in maternal plasma.

348 The changes in amniotic fluid thrombin generation were reported also in women with preterm

349 parturition. Indeed, intra-amniotic infection and/or inflammation is associated with an increased

350 amniotic fluid TAT III complexes (Fig. 7). This is important since it represents an increased

351 thrombin generation in the amniotic cavity during infection and/or inflammation that may

352 contribute to uterine contractility and the development of preterm birth[123]. Of interest, elevated

353 intra-amniotic TAT III concentrations were associated with a shorter amniocentesis to delivery

354 interval and an earlier gestational age at delivery only in patients with preterm labor without

355 intra-amniotic infection or inflammation[123]. This observation suggests that in a subset of patients

356 with preterm labor, activation of the coagulation system can generate preterm parturition and

357 delivery; while in those with intra-amniotic infection and/or inflammation the activation of the

358 coagulation and thrombin generation is a byproduct of the inflammatory process leading to

359 preterm birth.

360 This represents evidence of the activation and propagation of coagulation cascade, being

361 thrombin generation the witness of the former mechanisms and the inhibitor of the initiation

362 step[54].

363 **5. Conclusion**

364 The evidence presented herein suggests a role for increased thrombin generation and vascular

365 placental lesions in the pathogenesis of the great obstetrical syndromes. This process can be the

366 result of the contribution of procoagulant and vascular abnormalities as well as inflammatory and

367 infectious mechanisms, representing the starting point for pregnancy complications based on

368 vascular disease.

369 As presented, these changes affect the mother, the placenta, membranes and amniotic fluid.

370 Moreover, preliminary evidence suggest that some of the changes in the hemostatic system in the

371 mother and in the amniotic fluid predate the clinical presentation of the disease. Suggesting that

372 better understanding of the vascular and coagulation changes associated with the great obstetrical

373 syndromes may assist us in earlier detection and the development or introduction of therapeutic

374 modalities for these syndromes.

375

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728 (n=61). (c) Comparison of maternal plasma TFPI/TF ratio between women with normal

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741 atherosis of maternal arterioles in the placental membranes: a cluster of decidual arterioles shows

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748   maternal spiral arteries in the basal plate lack normal trophoblast remodeling and retain their pre-

749   pregnancy muscular media. Clusters of immature intermediate trophoblast and increased

750   placental giant cells are seen above and below the muscular arteries, respectively (X 10). d. Acute

751   atherosis of muscularized basal plate arteries with accompanying implantation site abnormalities:

752   three cross sections of a basal plate artery are seen. The two on the left show persistence of the

753   muscular media while the one on the right has undergone fibrinoid necrosis of the media with

754   foamy macrophages (acute atherosis). Clusters of immature intermediate trophoblast are also

755   seen overlying the arteries (X 4). e. Immature intermediate trophoblast: clusters of abnormally

756   small intermediate trophoblast with focal vacuolation are surrounded by an excessive amount of

757   basal plate fibrin. Increased placental site giant cells are also seen at the lower margin (X 10). f.

758   Increased placental site giant cells: numerous multinucleate placental site giant cells, not usually

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771   intervillous (and intravillous) fibrin: small aggregates of intervillous fibrin adhere to, and are

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777   Figure 6. Amniotic fluid tissue factor concentration among women with normal pregnancies

778   (median 3710.4 pg/ml, range 2198.8–6268) and patients with a fetal demise (median 8535.4

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781   81.6 pM, range 7.2–1603.4). From EREZ O, GOTSCH F, MAZAKI-TOVI S, et al. Evidence of

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Table 1

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	TF concentration and/or activity	TFPI concentration and/or activity	TAT III complexes concentration	Protein Z concentration	Thrombin generation	References
Premature rupture of membranes	Activity ↑ Concentration ↑	Concentration ↓	Concentration ↑	Concentration ↓	↑	1-5
Preterm labor	Activity ↑ Concentration =	Activity = Concentration ↓	Concentration ↑	Concentration ↓	↑	1-5
Fetal demise	Activity = Concentration =	Activity = Concentration ↓	Concentration ↑	Concentration ↓	↑	1-5
Preeclampsia	Activity ↑ Concentration ↑	Concentration ↑	Concentration ↑	Concentration ↓	↑	1-5
Intrauterine growth retardation	Concentration ↓	Concentration =	Concentration ↑	Concentration ↓	↑	1-5

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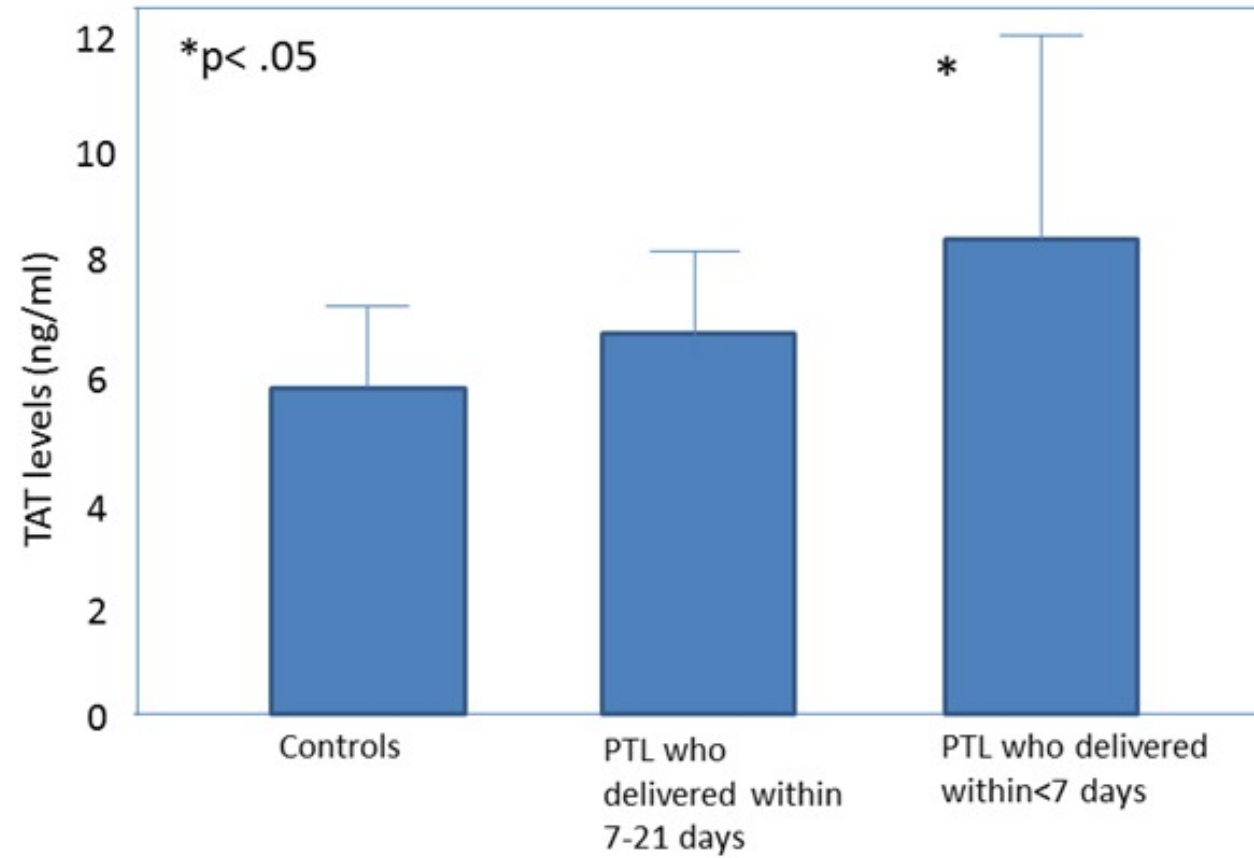
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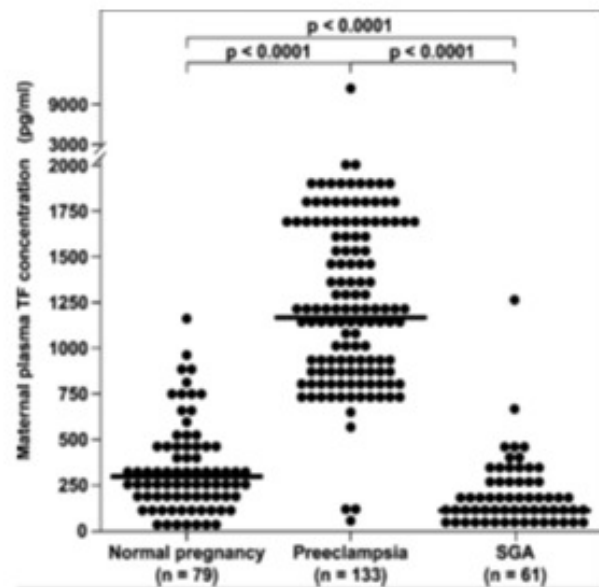
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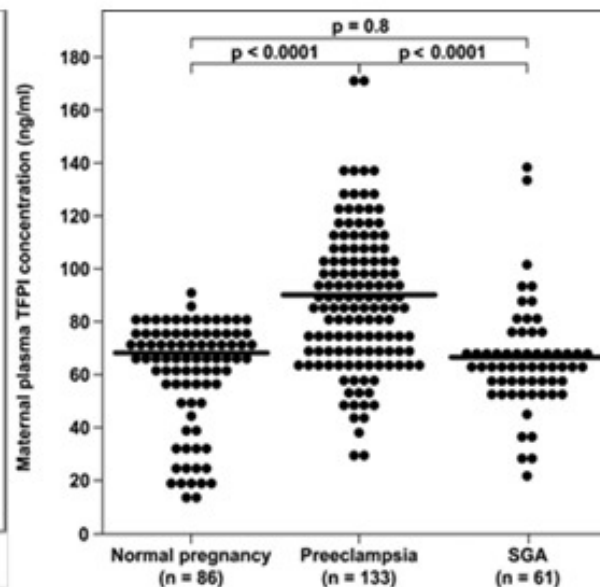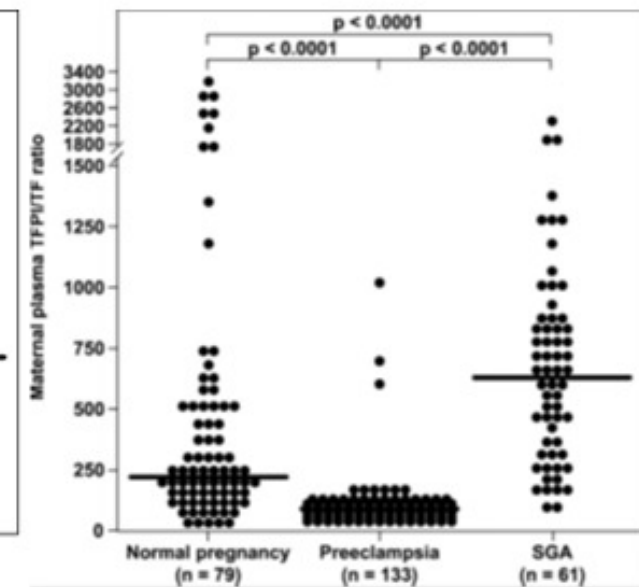
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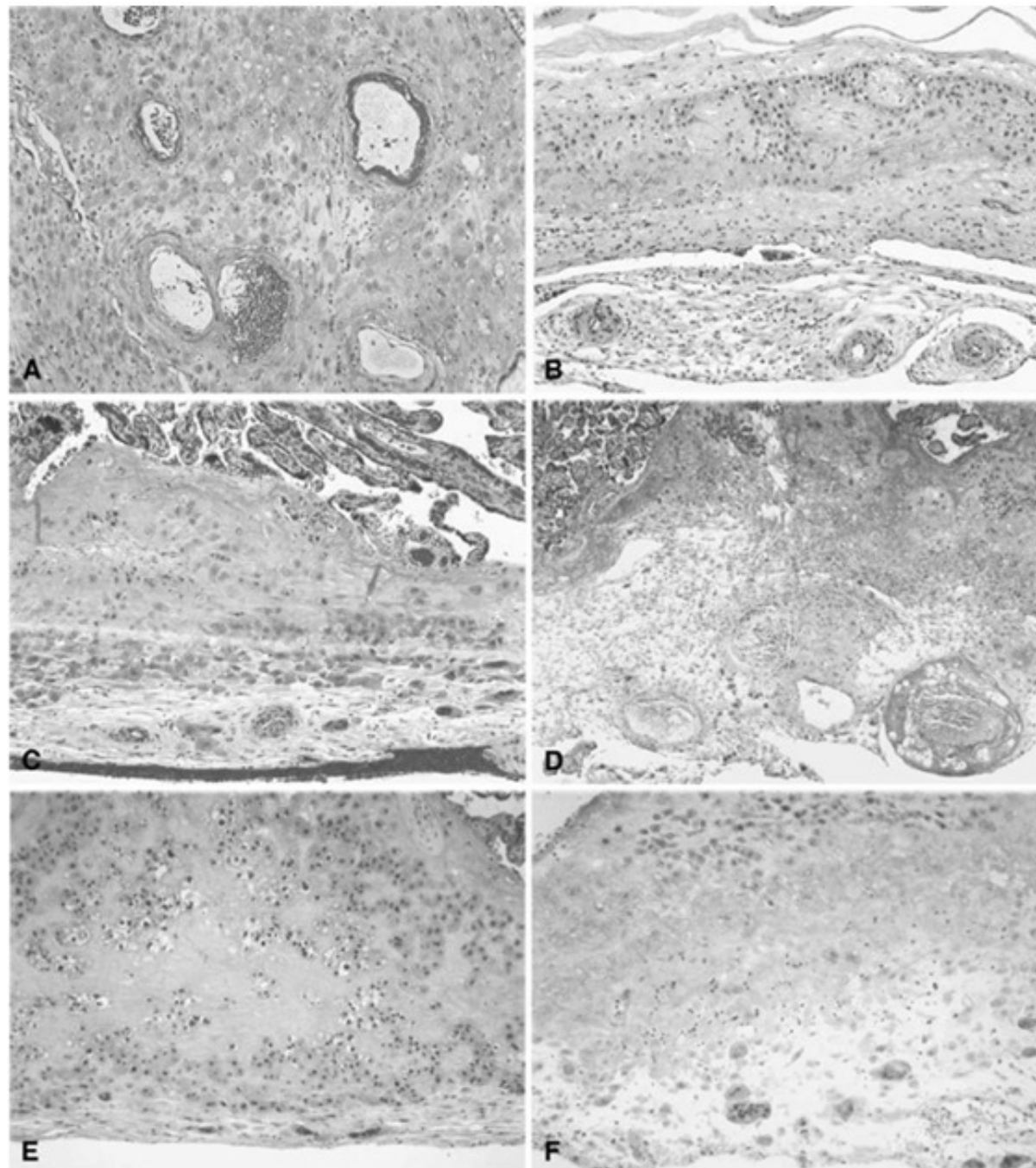
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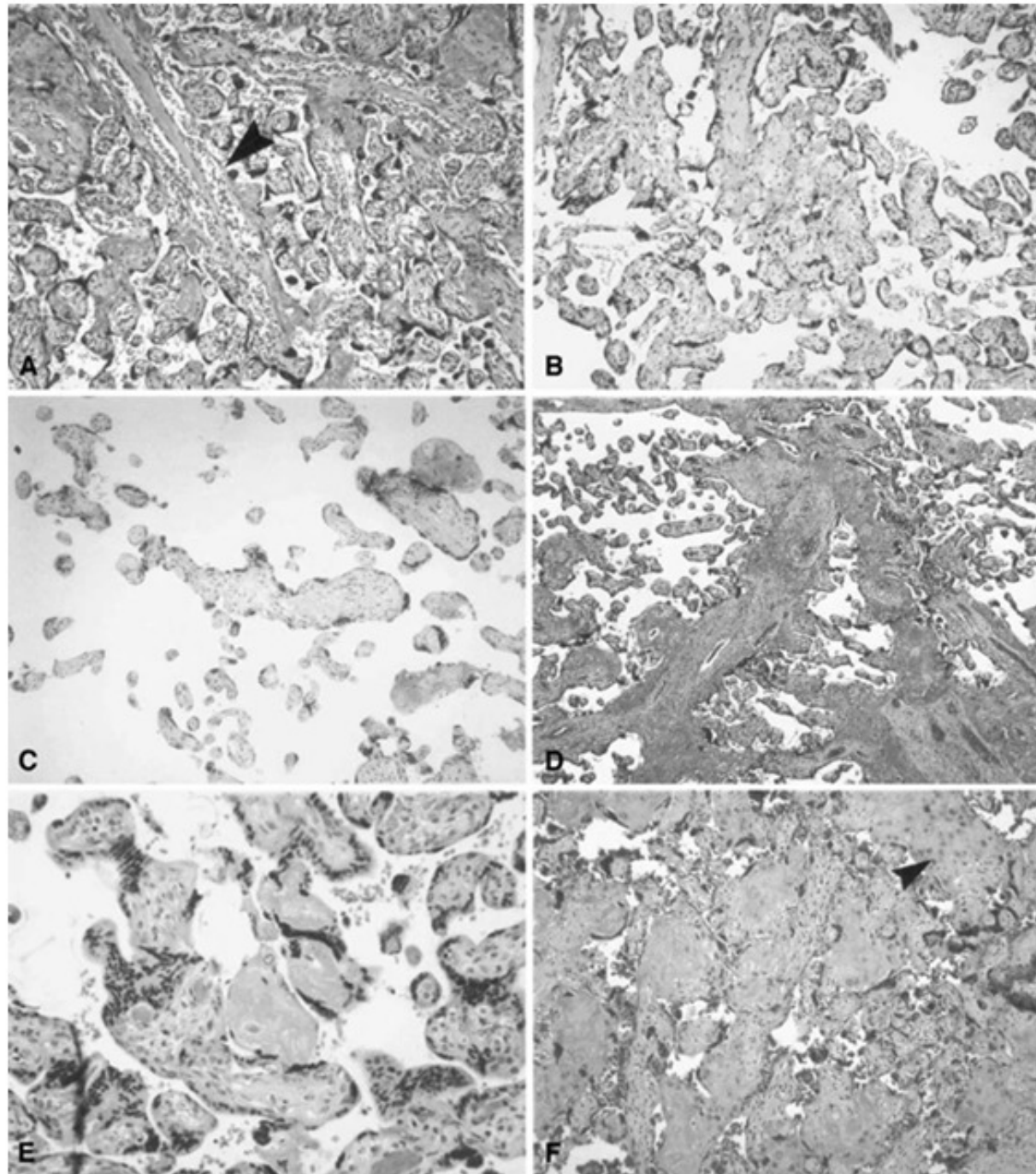
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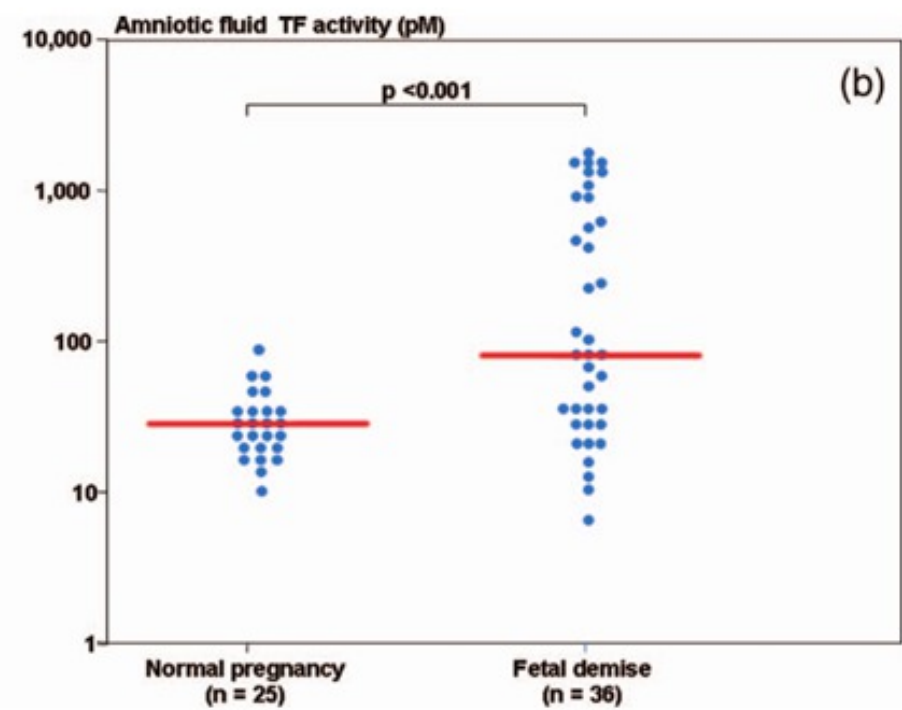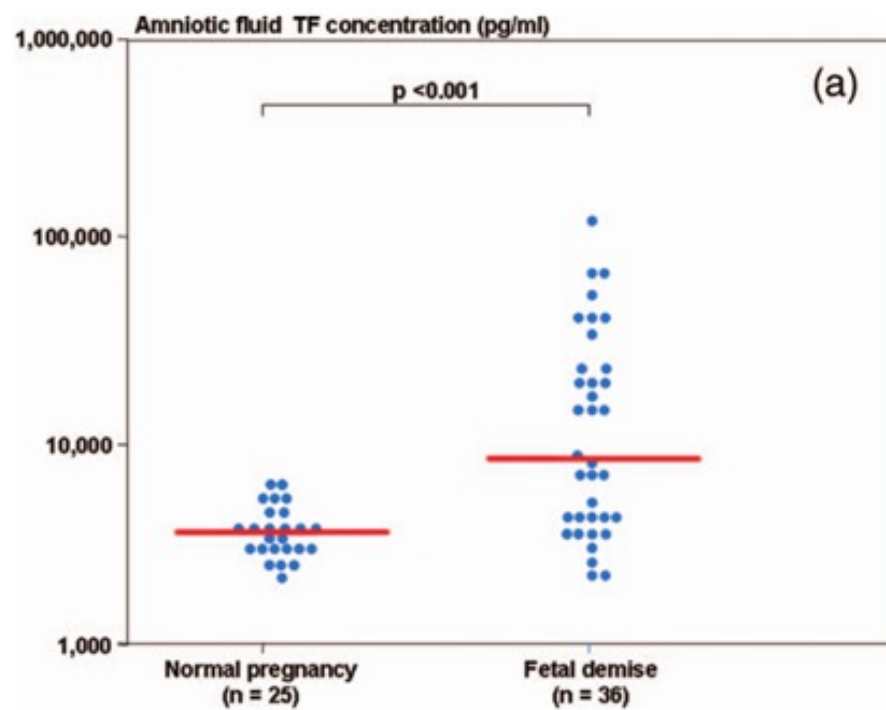
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