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## ORIGINAL ARTICLE

# Anti-BP180 IgG antibody ELISA values correlate with adverse pregnancy outcomes in pemphigoid gestationis

Nadège Cordel<sup>1,2</sup>  | Jasmine Flament<sup>3</sup> | Fabienne Jouen<sup>2,4</sup> | Vannina Seta<sup>5</sup> |  
 Emmanuelle Tancrede-Bohin<sup>6</sup> | Catherine Picard Dahan<sup>7</sup> | Maria-Polina Konstantinou<sup>8</sup>  |  
 Olivier Dereure<sup>9</sup>  | Gaëlle Quéreux<sup>10</sup> | Catherine Prost<sup>11</sup> | Christophe Bedane<sup>12</sup> |  
 Sébastien Debarbieux<sup>13</sup> | Jean-Philippe Lacour<sup>14</sup> | Anne Domp martin<sup>15</sup> |  
 Ewa Wierzbicka-Hainaut<sup>16</sup> | Isabelle Bourgault Villada<sup>17</sup> | Saskia Ingen Housz Oro<sup>18</sup>  |  
 Pierre Vabres<sup>19</sup> | Marie-Aleth Richard<sup>20</sup> | Emmanuel Delaporte<sup>21</sup> | Anne Pham-Ledard<sup>22</sup>  |  
 Marie-Thérèse Leccia<sup>23</sup> | Noémie Litrowski<sup>24</sup> | Catherine Michel<sup>25</sup> | Brigitte Lagrange<sup>26</sup> |  
 Michel D'Incan<sup>27</sup> | Claire Abasq<sup>28</sup> | Sophie Duvert-Lehembre<sup>29</sup> | Alain Dupuy<sup>30</sup> |  
 Isabelle Alcaraz<sup>31</sup> | Anne-Laure Breton-Guitarian<sup>32</sup> | Florian Lombart<sup>33</sup> | Eric Estève<sup>34</sup> |  
 Laurent Machet<sup>35</sup>  | Pascal Del Giudice<sup>36</sup> | Marion Fenot<sup>37</sup> | Thibaut Belmondo<sup>38</sup> |  
 Florence Morin<sup>39</sup> | Olivia Guérin<sup>40</sup> | Jacques Benichou<sup>40,41</sup> | Benoît Tressières<sup>42</sup> |  
 Pascal Joly<sup>2,3</sup>  | for the French study Group on autoimmune bullous skin diseases

<sup>1</sup>Department of Dermatology and Clinical Immunology, Guadeloupe University Hospital, Pointe-à-Pitre, Guadeloupe

<sup>2</sup>Univ Rouen Normandie, FOCIS Center of Excellence PAN'THER, Rouen, France

<sup>3</sup>Department of Dermatology, Rouen University Hospital, Rouen, France

<sup>4</sup>Department of Immunology and biotherapies, Rouen University Hospital, Rouen, France

<sup>5</sup>Department of Dermatology, Cochin Hospital AP-HP, Paris, France

<sup>6</sup>Department of Dermatology, Saint Louis Hospital AP-HP, Paris, France

<sup>7</sup>Department of Dermatology, Bichat Hospital AP-HP, Paris, France

<sup>8</sup>Department of Dermatology, Toulouse University Hospital, Toulouse, France

<sup>9</sup>Department of Dermatology, Saint-Eloi University Hospital, Montpellier, France

<sup>10</sup>Department of Dermatology, Nantes University Hospital, Nantes, France

<sup>11</sup>Department of Dermatology, Avicenne Hospital AP-HP, Bobigny, France

<sup>12</sup>Department of Dermatology, Limoges University Hospital, Limoges, France

<sup>13</sup>Department of Dermatology, Hôtel Dieu Hospital, Lyon, France

<sup>14</sup>Department of Dermatology, University Hospital of Nice, Nice, France

<sup>15</sup>Department of Dermatology, Caen University Hospital, Caen, France

<sup>16</sup>Department of Dermatology, Poitiers University Hospital, Poitiers, France

<sup>17</sup>Department of Dermatology, Ambroise Paré Hospital, AP-HP, Boulogne-Billancourt, France

<sup>18</sup>Department of Dermatology, Henri Mondor Hospital, AP-HP and Univ Paris Est Créteil, EpidermE, Créteil, France

<sup>19</sup>Department of Dermatology, Dijon University Hospital, Dijon, France

<sup>20</sup>Department of Dermatology, La Timone University Hospital APHM, Marseille, France

<sup>21</sup>Department of Dermatology, UMR 7268 and North University Hospital APHM, Marseille, France

<sup>22</sup>Department of Dermatology, University Hospital of Bordeaux, Saint-André Hospital, Bordeaux, France

Nadège Cordel and Jasmine Flament: co-first authors.

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<sup>23</sup>Department of Dermatology, Allergology and Photobiology, Grenoble University Hospital, Grenoble, France

<sup>24</sup>Department of Dermatology, Monod General Hospital, Le Havre, France

<sup>25</sup>Department of Dermatology, Emile Muller Hospital, Mulhouse, France

<sup>26</sup>Department of Dermatology, Henri-Duffaut Hospital, Avignon, France

<sup>27</sup>Department of Dermatology, Clermont-Ferrand University Hospital, Clermont-Ferrand, France

<sup>28</sup>Department of Dermatology, Brest University Hospital, Brest, France

<sup>29</sup>Department of Dermatology, Dunkerque Hospital, Dunkerque, France

<sup>30</sup>Department of Dermatology, Rennes University Hospital, Rennes, France

<sup>31</sup>Department of Infectious diseases and Travel, Gustave Dron Hospital, Tourcoing, France

<sup>32</sup>Department of Dermatology, Saint-Luc Saint-Joseph Hospital, Lyon, France

<sup>33</sup>Department of Dermatology, Amiens University Hospital, Amiens, France

<sup>34</sup>Department of Dermatology, Orléans Regional Hospital, Orléans, France

<sup>35</sup>Department of Dermatology, Tours University Hospital, Tours, France

<sup>36</sup>Infectiology-Dermatology Unit, Intercommunal Hospital of Fréjus Saint Raphaël, Fréjus, France

<sup>37</sup>Department of Dermatology, Departmental Hospital of Vendée, La Roche-sur-Yon, France

<sup>38</sup>Department of Immunology, Henri Mondor Hospital, AP-HP, Créteil, France

<sup>39</sup>Department of Immunology, Saint-Louis Hospital AP-HP, Paris, France

<sup>40</sup>Department of Biostatistics, Rouen University Hospital

<sup>41</sup>Univ Rouen Normandie, IRIB, Inserm U1219, Rouen, France

<sup>42</sup>Centre d'Investigation Clinique Antilles Guyane, INSERM CIC 1424, Pointe-à-Pitre, Guadeloupe

### Correspondence

Nadège Cordel, Department of Dermatology and Clinical Immunology, Guadeloupe University Hospital, Pointe-à-Pitre, Guadeloupe, BP 465, 97159 Pointe-à-Pitre cedex, France.

Email: [nadege.cordel@chu-guadeloupe.fr](mailto:nadege.cordel@chu-guadeloupe.fr)

### Abstract

**Background:** Adverse pregnancy outcomes (APO) occur in 35% of patients with pemphigoid gestationis (PG). No biological predictor of APO has been established yet.

**Objectives:** To assess a potential relationship between the occurrence of APO and the serum value of anti-BP180 antibodies at the time of PG diagnosis.

**Methods:** Multicentre retrospective study conducted from January 2009 to December 2019 in 35 secondary and tertiary care centres. Inclusion criteria: (i) diagnosis of PG according to clinical, histological and immunological criteria, (ii) ELISA measurement of anti-BP180 IgG antibodies determined at the time of PG diagnosis with the same commercial kit and (iii) obstetrical data available.

**Results:** Of the 95 patients with PG included, 42 had one or more APO, which mainly corresponded to preterm birth ( $n = 26$ ), intrauterine growth restriction (IUGR) ( $n = 18$ ) and small weight for gestational age at birth ( $n = 16$ ). From a ROC curve, we identified a threshold of 150 IU ELISA value as the most discriminating to differentiate between patients with or without IUGR, with 78% sensitivity, 55% specificity, 30% positive and 91% negative predictive value. The threshold >150 IU was confirmed using a cross-validation based on bootstrap resampling, which showed that the median threshold was 159 IU. Upon adjusting for oral corticosteroid intake and main clinical predictors of APO, an ELISA value of >150 IU was associated with the occurrence of IUGR (OR = 5.11; 95% CI: 1.48–22.30;  $p = 0.016$ ) but not with any other APO. The combination of blisters and ELISA values higher than 150 IU led to a 2.4-fold higher risk of all-cause APO (OR: 10.90; 95% CI: 2.33–82.3) relative to patients with blisters but lower values of anti-BP180 antibodies (OR of 4.54; 95% CI 0.92–34.2).

**Conclusion:** These findings suggest that anti-BP180 antibody ELISA value in combination with clinical markers is helpful in managing the risk of APO, in particular IUGR, in patients with PG.

## INTRODUCTION

Pemphigoid gestationis (PG) is a rare pregnancy-associated autoimmune bullous disease. Its incidence ranges between 1/20 000 and 1/50 000 pregnancies.<sup>1</sup> The disease most frequently begins in the second or the third trimester of

pregnancy. PG can be associated with adverse pregnancy outcomes (APO) such as preterm birth and decreased gestational age at delivery in 34% to 37% of cases among the series.<sup>2–4</sup> Chi et al. reported that APO were associated with early onset of PG and presence of blisters, which are both markers of the severity of PG.<sup>4</sup>

PG is associated with the production of autoantibodies directed against the NC16A epitope of BP180, a transmembrane protein of the hemidesmosomes.<sup>5,6</sup> We recently showed the high sensitivity and specificity of enzyme-linked immunosorbent assay (ELISA) assay for the detection of anti-BP180 antibodies in patients with PG.<sup>7</sup> Additionally, the serum level of PG anti-BP 180 antibodies seems to correlate with the disease activity according to the literature data.<sup>7–10</sup>

Huilaja et al. found that BP-180 was expressed in PG amniotic membranes even during the first trimester<sup>11</sup> and anti-BP180 antibodies IgG1 deposits have been observed on the basement membrane of placentas in PG patients.<sup>12</sup> Moreover, mild villitis and immature villous structures have been observed in PG placentas, which suggests that anti-BP180 antibodies might induce epithelial-stromal microseparation in placenta, and lead to placenta functional failure.<sup>11</sup>

To assess a potential relationship between the occurrence of APO and anti-BP180 antibodies, we assessed the association between anti-BP180 IgG antibody ELISA values at the time of PG diagnosis and the occurrence of APO in 95 patients with PG.

## PATIENTS AND METHODS

### Study oversight and participants

We conducted a retrospective study in eight general hospitals and 27 university hospitals in France. This study was approved by the Institutional Review Board of Rouen University Hospital (N°E2021–34). Inclusion criteria were as follows: (i) patients with a diagnosis of PG occurring during pregnancy, based on suggestive clinical features (blisters and/or urticarial skin lesions), (ii) direct immunofluorescence showing IgG and/or C3 deposit along the dermal-epidermal junction, (iii) detection of anti-BP180 IgG antibodies by ELISA (commercial kit Euro-immun threshold min 20 IU/ml-max 200 IU/ml) performed at the time of PG diagnosis and (iv) patients' clinical characteristics and evolutive data available from the beginning to the end of the pregnancy. Patients whose PG started after delivery were excluded.

### Study assessments and outcomes

Patients with PG followed between 1 January 2009 and 31 December 2019 in the participating centres were identified using the computerized database of the immunology laboratory of the French reference centre for autoimmune bullous skin diseases in Rouen. The available serum samples with a BP180 ELISA value equal to or higher than 200 IU, which corresponds to the highest quantitative value measurable by the commercial kit used, were secondarily diluted in accordance with the recommendations of the reagent manufacturer, in order to determine the precise anti-BP180 antibody titers.

Patients' clinical characteristics at diagnosis and their clinical course were retrospectively retrieved from dermatology and obstetrical medical records.

Pregnancy outcomes reported to be associated with PG in the literature were recorded, that is prematurity (birth before 37 weeks of pregnancy), intrauterine growth restriction (IUGR, i.e. a pathological growth restriction, with an estimated birth weight below the 10<sup>th</sup> percentile for gestational age), small for gestational age at birth (i.e. birth weight below the 10<sup>th</sup> percentile), preterm labour (i.e. regular contractions and concomitant cervical changes), spontaneous miscarriage (early or late) and in utero foetal death.

Additional factors potentially responsible for adverse pregnancy outcomes such as intake of oral corticosteroids, diabetes mellitus, arterial hypertension and infection were also recorded.

### Statistical analysis

Quantitative variables were summarized as mean  $\pm$  standard deviation or median with interquartile range (IQR) depending on their distribution (graphical verification and Kolmogorov–Smirnov test) with corresponding 95% confidence interval (CI) and compared between groups using the Mann–Whitney nonparametric test. Categorical data were expressed as percentages and compared between groups using Pearson's chi-square test or Fisher's exact test, as appropriate. Logistic regression models were used to estimate crude and adjusted odds ratios (OR) with corresponding 95% CI.

A receiver operating characteristic (ROC) curve was estimated, to help determine optimal cut-off values of baseline anti-BP180 ELISA values to predict the occurrence of IUGR. The area under the ROC curve (AUC) was estimated along with the corresponding 95% CI, and the estimated AUC was compared to 0.5 to assess the overall diagnostic value. The threshold that produced the highest sum of sensitivity and specificity (i.e. highest Youden's index) was considered the most discriminating. Internal cross-validation of optimal threshold selection based on bootstrap resampling was performed using 2000 bootstrap replicates.

All statistical analyses were performed using SAS version 9.4 software (SAS Institute) and R software (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>). For all analyses, a *p*-value less than 0.05 was considered statistically significant.

## RESULTS

### Baseline characteristics and clinical course of patients

Among the 115 patients with PG identified from the database, five patients had a PG which started after delivery, one patient had a voluntary termination of pregnancy, and

the outcome of pregnancy could not be recorded in 14 patients. Finally, 95 women with PG of which 19 were primiparous were included and analysed. Their mean age was  $32.9 \pm 6.0$  years, which was slightly older than the 30.3 years mean age of pregnant women in France.

Main clinical data are summarized in [Table 1](#).

Median anti-BP180 antibody ELISA value at the time of diagnosis was 144 IU (IQR 96–186; 95% CI: 122–166). Patients with blisters had higher anti-BP180 ELISA values than those without blisters (median 159 IU; IQR 112–192; 95% CI 129–180 vs. 104 IU; IQR 84–144; 95% CI: 83–144;  $p = 0.008$ ).

A total of 42 patients had one or more APO. Main causes of APO were prematurity ( $n = 26$ ), IUGR ( $n = 18$ ) and small for gestational age at birth ( $n = 16$ ). Main risk factors for the occurrence of APO are mentioned in [Table 1](#).

Patients with all-cause APO and to a lesser degree patients with premature delivery had blistering lesions more frequently than those with good pregnancy outcomes 88.1% versus 69.8%,  $p = 0.033$  and 88.5% versus 70.5%,  $p = 0.073$ , respectively.

### Assessment of the predictive value of anti-BP180 antibody ELISA values for the occurrence of adverse pregnancy outcome

Median anti-BP180 antibody ELISA values of patients with or without APO were 160 IU (IQR 116–190 IU; 95% CI 124–180) versus 131 IU (IQR 92–182 IU; 95% CI 112–160) ( $p = 0.234$ ).

We then assessed the median anti-BP180 antibody ELISA values separately in patients who had the most frequently observed APO, corresponding to prematurity, IUGR and small for gestational age at birth, despite the relatively limited number of patients from 16 to 26 in each group ([Table 2](#)).

Patients with IUGR tended to have higher median anti-BP180 antibody values than patients with normal intra-uterine growth curves, 176 IU (IQR 134–208 IU; 95% CI: 118–210) versus 132 IU (IQR 94–181 IU; 95% CI: 115–160) although this trend was not significant ( $p = 0.111$ ).

To determine the subpopulation of PG patients who were at a higher risk of IUGR, a ROC curve was estimated to help to determine cut-off values of anti-BP180 antibody ELISA values predictive for the occurrence of IUGR ([Figure 1](#)). Discrimination between patients with or without IUGR was moderate (AUC = 0.63 95% CI: 0.46–0.80). Using Youden's index, we identified that a baseline anti-BP180 antibody ELISA value of 150 IU was the most discriminating to differentiate between patients with or without IUGR, with 78% sensitivity, 55% specificity, 30% positive and 91% negative predictive value and highest Youden's index of 0.33 for the occurrence of IUGR. There were 14/18 (77.8%) patients with IUGR versus 33/74 without IUGR (44.6%) with value of at least 150 IU ( $p = 0.012$ ) corresponding to a crude OR of 4.35; 95% CI: 1.41–16.5;  $p = 0.017$ . This difference was confirmed in multivariate analysis upon adjusting for oral corticosteroid intake, trimester of pregnancy at diagnosis and clinical

blistering lesions (adjusted OR = 5.11; 95% CI: 1.48–22.30;  $p = 0.016$ ).

Since the ROC curve did not show a clear inflexion point, we also examined the accuracy of a higher anti-BP180 antibody ELISA value of 200 IU, which corresponds to the highest quantifiable value of the ELISA commercial kit used. A baseline anti-BP180 antibody ELISA value of 200 IU or more provided 44% sensitivity, 82% specificity, 38% positive and 86% negative predictive value and a Youden's index of 0.26 corresponding to an adjusted OR of 3.84; 95% CI: 1.14–13.40;  $p = 0.030$  for the occurrence of IUGR.

Cross-validation based on bootstrap resampling identified a threshold of 150 IU of anti-BP180 antibody ELISA value as optimal in 30.5% of bootstrap replicates ([Figure 2](#)). The median threshold was 159 IU (IQR: 151–184 IU). The range of anti-BP180 antibody ELISA value between 150 and 200 IU included 71.3% of bootstrap replicates.

Patients who had both risk factors of APO (i.e. an anti-BP180 antibody ELISA value higher than 150 IU and clinical blistering lesions) had a 2.4 higher risk of all-cause APO relative to those with only the clinical predictor (i.e. blisters): adjusted ORs of 10.90; 95% CI: 2.33–82.3; and 4.54; 95% CI: 0.92–34.2, respectively.

## DISCUSSION

This study suggests that the measurement anti-BP180 antibody ELISA values determined at the time of diagnosis may be a valuable biomarker in addition to the presence of clinical blisters to predict the occurrence of APO in patients with PG.

In our series, the proportions of main types of APO (prematurity, small-for-gestational-age at birth) were close to those reported in two large series of PG in the literature though the proportion of IUGR was not reported in those series.<sup>4,13</sup> The higher frequency of all-cause APO in patients whose PG started during the first or second trimester of pregnancy that we observed in our series was also consistent with the literature.<sup>4</sup>

We confirmed the findings by Chi C et al. who identified the presence of blistering lesions as a predictor for the occurrence of APO. In their series, the presence of blisters was associated with a decreased gestational age at delivery and prematurity but they did not evidence any relationship with other APO, including small for gestational age at birth.<sup>4</sup> Unfortunately, anti-BP180 antibody ELISA values were not recorded in their study. As previously described, we observed that patients with blistering lesions had higher anti-BP180 antibody ELISA values than those with nonblistering PG which corroborate the correlation between high level of anti-BP 180 antibodies and the severity of the maternal disease reported in the literature.<sup>7–10</sup>

We observed that anti-BP180 antibody ELISA values higher than 150 IU were only associated with the occurrence of IUGR, while we did not evidence any relationship between these anti-BP180 ELISA values and other types of APO such as prematurity or small for gestational age at birth.

**TABLE 1** Main clinical characteristics of the 95 PG patients.

	Total	APO <sup>a</sup>		p-value
		No	Yes	
N	95	53	42	
Age at diagnosis of PG	32.9 +/- 6.0	33.2 +/- 6.4	32.5 +/- 5.5	0.747
95% CI	[31.6; 34.1]	[31.4; 35.0]	[30.8; 34.2]	
Unknown	0			
Diabetes mellitus (medical history or gestational)	16 (17.0%)	10 (18.9%)	6 (14.6%)	0.588
Unknown	1		1	
Hypertension (medical history or gestational)	5 (5.3%)	3 (5.7%)	2 (4.9%)	>0.999
Unknown	1		1	
Infection during pregnancy	7 (7.7%)	2 (3.8%)	5 (12.8%)	0.134
Unknown	4	1	3	
Corticosteroid intake	47 (49.5%)	22 (41.5%)	25 (59.5%)	0.081
Unknown	0			
Trimester of pregnancy at diagnosis of PG				0.001
1st	6 (6.1%)	1 (1.9%)	5 (12.2%)	
2nd	44 (47.3%)	19 (36.5%)	25 (61.0%)	
3rd	43 (46.2%)	32 (61.5%)	11 (26.8%)	
Unknown	2	1	1	
Presence of bullae	74 (77.9%)	37 (69.8%)	37 (88.1%)	0.033
Unknown	0			
If bullae, number				0.254
<10 bullae	50 (69.4%)	29 (78.4%)	21 (60.0%)	
[10–50] bullae	13 (18.1%)	5 (13.5%)	8 (22.9%)	
> 50 bullae	9 (12.5%)	3 (8.1%)	6 (17.1%)	
Unknown	2	0	2	
Prematurity	26 (28.9%)	0 (0.0%)	26 (70.3%)	<0.001
+ other(s) APO	11		11	
Not applicable (without delivery) - Unknown	4–1	0–0	4–1	
Intrauterine growth restriction-IUGR	18 (19.6%)	0 (0.0%)	18 (46.2%)	<0.001
+ other(s) APO	15		15	
Not applicable (without delivery) - Unknown	1–2	0–0	1–2	
Small for gestational age at birth-SGA	16 (19.8%)	0 (0.0%)	16 (47.1%)	<0.001
+ other(s) APO	13(11 IUGR)		13	
Not applicable (without delivery) - Unknown	1–13	0–6	1–7	
Preterm labour	4 (4.3%)	0 (0.0%)	4 (10.0%)	0.031
+ other(s) APO	3		3	
Not applicable (without delivery) - Unknown	0–2	0–0	0–2	
Late spontaneous miscarriage	1 (1.1%)	0 (0.0%)	1 (2.4%)	0.442
+ other(s) APO	0			
Not applicable (without delivery) - Unknown	0–0			
In utero foetal death	3 (3.2%)	0 (0.0%)	3 (7.1%)	0.083
+ other(s) APO	2 (IUGR)		2	
Not applicable (without delivery) - Unknown	0–0			

<sup>a</sup>Missing data for five patients who had delivery of an alive baby without information for IUGR, SGA, preterm labour or prematurity.

**TABLE 2** Comparison of anti-BP180 ELISA values in patients with and without adverse pregnancy outcome (APO).

Patients with APO ( <i>n</i> )	Not applicable -not known	Yes	No	<i>p</i> -value
		<i>n</i> Median. (Q1–Q3) [95% CI]	<i>n</i> Median. (Q1–Q3) [95% CI]	
Patients with one or more APO	0–0	42 160 (116–190) [124; 180]	53 131 (92–182) [112; 160]	0.234
Prematurity	4 <sup>a</sup> –1 <sup>b</sup>	26 148 (114–190) [114; 190]	61 130 (91–178) [112; 160]	0.545
Intrauterine growth restriction-IUGR	1 <sup>c</sup> –2 <sup>d</sup>	18 176 (134–208) [118; 210]	74 132 (94–181) [115; 160]	0.111
Small for gestational age at birth-SGA	1 <sup>c</sup> –13 <sup>e</sup>	16 155 (120–206) [76; 250]	65 136 (91–183) [112; 168]	0.499
Preterm labour	0–2 <sup>f</sup>	4 127 (98–268) Not calculable	89 144 (95–187) [122; 168]	0.941
Late spontaneous miscarriage	0–0	1 <sup>g</sup>	94 144 (96–186) [122; 166]	Not calculable
In utero foetal death	0–0	3 184 (180–194) Not calculable	92 141 (94–184) [121; 160]	0.120

<sup>a</sup>Four patients without delivery (late spontaneous miscarriage *n* = 1, in utero foetal death *n* = 3).

<sup>b</sup>One patient for whom the data are missing for prematurity.

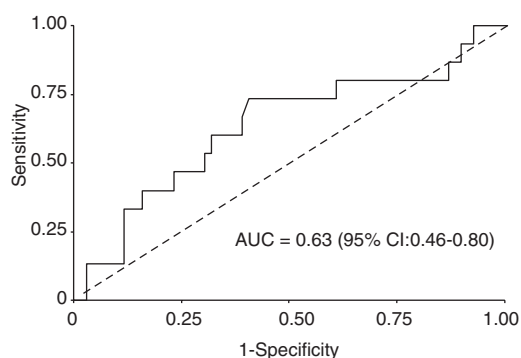
<sup>c</sup>One patient with late spontaneous miscarriage.

<sup>d</sup>Two patients for whom the data are missing for IUGR.

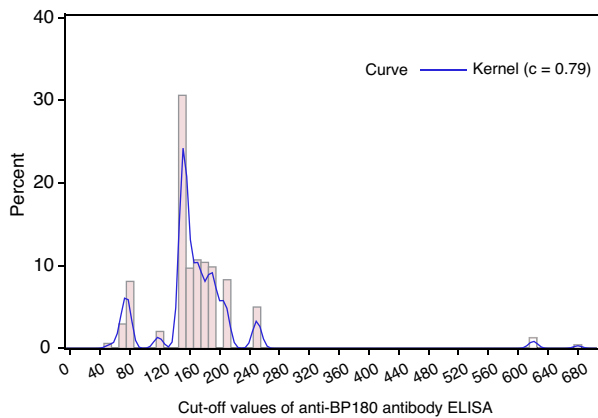
<sup>e</sup>Thirteen patients for whom the data are missing for SGA.

<sup>f</sup>Two patients for whom the data are missing for preterm labour.

<sup>g</sup>Serum sample with a BP180 ELISA value equal to or higher than 200 IU (which corresponds to the highest quantifiable value of the commercial kit used) not available for dilution.

**FIGURE 1** ROC curve-IUGR.

We estimated that a threshold of 150 IU of anti-BP180 ELISA value provided a 30% positive and 91% negative predictive value with an adjusted OR = 5.11 (95% CI: 1.48–22.30;  $p = 0.016$ ) for the occurrence of IUGR. This threshold might be of interest for clinicians, given the low risk of IUGR in patients with an anti-BP180 antibody ELISA value lower than 150 IU, which may somehow reassure patients on the likely good outcome of their pregnancy. The higher ELISA value of 200 IU that we also examined only slightly increased the positive predictive value for the occurrence of IUGR from 30% to 38% while provided a slightly lower negative predictive value (86% vs. 91%) with an adjusted OR of 3.84; 95% CI: 14–13.40;  $p = 0.030$ . This result suggests to rather consider the 150 IU threshold from which the close monitoring



**FIGURE 2** Distribution bootstrap cut-off values of anti-BP180 IgG antibody ELISA for the occurrence of IUGR.

of patients at high risk of IUGR is required according to the recommendations of the international guidelines.<sup>14</sup>

Interestingly, the presence of both risk factors of APO (i.e. anti-BP180 antibody values higher than 150 IU and clinical blisters) provided a twofold increased risk of all-cause APO relative to patients with only the clinical predictor (presence of blistering lesions), which emphasizes the interest of the measurement of anti-BP 180 antibodies and strongly suggests considering the combination of these two predictors for the management of PG patients.

This study has some limitations. First, the optimal threshold that was selected from the ROC curve analysis and using the Youden's index should be considered with caution; in particular, the 150 IU threshold for the occurrence of IUGR should not be taken at face value in view of cross-validation analysis showing substantial variability in optimal threshold selection. Rather, any threshold in the range of 150 to 200 IU could be considered as optimal at this stage. In view of this uncertainty, one might argue to feel more reasonable to propose a discriminating value corresponding to a range of anti-BP180 antibody ELISA value between 150 and 200 IU since this interval included the optimal threshold in 71.3% of bootstrap replicates. Second, we could not assess the potential interest of the anti-BP180 antibody change over time in this retrospective study, in which serum samples were collected only once at the time of diagnosis. In particular, one might hypothesize that the persistence of high levels of anti-BP180 antibody values under treatment might have a deleterious prognostic effect. Finally, despite a rather large sample of 95 patients for such a rare disease as PG, the study lacks power in view of the rather small number of patients from 1 to 26 in each type of APO and this may explain why many intergroup differences were only borderline significant.

## CONCLUSION

Overall, this study based on a large series of patients with PG suggests considering anti-BP180 IgG antibody ELISA values as a biological predictor of APO, especially IUGR, helpful

in combination with clinical markers (i.e. presence of blisters and early onset of the disease) to manage these patients. The identified thresholds should ideally be tested on another retrospective cohort of patients with PG since a prospective study is unlikely, given the rarity of the disease.

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None.

## CONFLICTS OF INTEREST STATEMENT

None to declare.

## DATA AVAILABILITY STATEMENT


The data that support the findings of this study are available from the corresponding author, [NC], upon reasonable request.

## IRB APPROVAL

This study was approved by the institutional review board of Rouen University Hospital (N°E2021–34).


## ORCID

Nadège Cordel  <https://orcid.org/0000-0003-1679-8005>

Maria-Polina Konstantinou  <https://orcid.org/0000-0001-8171-6542>

Olivier Dereure  <https://orcid.org/0000-0001-8736-1922>

Saskia Ingen Housz Oro  <https://orcid.org/0000-0002-5383-7096>

Anne Pham-Ledard  <https://orcid.org/0000-0003-2960-6084>

Laurent Machet  <https://orcid.org/0000-0001-5985-878X>

Pascal Joly  <https://orcid.org/0000-0002-5734-0255>

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