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INVESTIGATIVE REPORT

Gestational Pemphigoid: Placental Morphology and Function

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Gestational pemphigoid (PG), a very rare pregnancy-associated bullous dermatosis, is associated with adverse pregnancy outcome (miscarriage, preterm delivery, foetal growth restriction). The major antigen in PG is collagen XVII (BP180). PG autoantibodies cross-react with collagen XVII in the skin and have been suggested to cause placental failure. On this basis, we evaluated clinical outcome and morphological and functional placental data of 12 PG pregnancies in Finland during 2002 to 2011. The placental-to-birth weight ratio was abnormal in half of the pregnancies. Ultrastructural analysis of PG placentas showed detachment of basement membranes and undeveloped hemidesmosomes. Ultrasound evaluations of placental function prior to delivery were normal in all but one pregnancy. Three (25%) neonates were delivered preterm after 35 gestational weeks and one pregnancy was complicated by preeclampsia and severe foetal growth restriction. Neonatal outcome was uneventful in every case. In conclusion, in pregnancies complicated by PG, slight alteration in ultrastructural morphology of the placental basement membrane was detected, but umbilical artery Doppler evaluation indicated no functional placental changes. ***Key words: pemphigoid gestationis; BP180; collagen XVII; placenta; umbilical artery; ultrasound; pregnancy outcome*****.**

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Pemphigoid gestationis (PG) is a rare pregnancy-associated bullous dermatosis with an incidence of approximately 1:50,000 pregnancies (1). It typically manifests in the second and third trimesters, but may develop at any stage during pregnancy and puerperium. Clinically, PG is characterized by severe pruritus, urticarial papules, plaques and subsequent blister development. The diagnostic hallmark of PG is linear C3 deposition along the basement membrane in the immunofluorescence staining of perilesional skin. Concomitant IgG depositions and circulating serum IgG autoantibodies are also typical for PG (2, 3). The major antigen in PG is collagen XVII (BP180), which is a transmembrane component of the hemidesmosome complex mediating the adhesion of epithelial cells to the basement membrane (4–6). Collagen XVII is predominantly expressed in skin, but is also present in amniotic epithelia, placenta and amniotic fluid (7, 8). In PG, autoantibodies are mainly targeted against the largest non-collagenous domain NC16A (9–12). The exact pathomechanism of PG remains unclear, but abnormal expression of MCH II (major histocompatibility complex) molecules in PG placenta has been suggested to trigger local allogeneic reaction against the feto-placental unit (13). PG autoantibodies are thought to cause placental failure and cross-react with collagen XVII in skin (14, 15). In clinical practice, PG does not increase foetal mortality, but an association with miscarriage, preterm delivery and foetal growth restriction has been reported (16–18).

Due to a possible placental failure and the known association of PG with placenta-originated adverse pregnancy outcomes, we wanted to evaluate morphological and functional placental data as well as the clinical outcome of 12 PG pregnancies in Finland during 2002 to 2011.

MATERIALS AND METHODS

Patients

Finnish dermatologists in all university and central hospitals were informed about this prospective PG study, which was approved by the ethics committee of Northern Ostrobothnia Hospital District, Oulu, Finland. Ten Finnish (Caucasian) patients with 12 pregnancies were recruited, and an informed consent was requested after the confirmation of PG diagnosis in the local units in 2002 to 2011. Inclusion criteria included typical cutaneous findings for PG and C3 positivity in direct immunofluorescence analysis of perilesional skin. Direct immunofluorescence analysis of skin and placental (patient 7) samples were performed using standard procedures. Clinical outcome data was collected from the patient records. The study was performed according to the Declaration of Helsinki 1983 and approved by the ethics committee of Northern Ostrobothnia Hospital District (reference number 61/2004). In addition, all participating women gave informed consent for use of their medical data for research purposes.

Blood sampling and transmission electron microscopy of the placenta

Circulating antibodies against collagen XVII were analysed in 6 out of 12 pregnancies by BP180-ELISA (Medical & Biological Laboratories, Nagoya, Japan) performed at HUSLAB in Helsinki, Finland.

Transmission electron microscopic analysis of placental samples from 5 PG placentas and control placentas collected from uneventful pregnancies at Oulu University Hospital, Oulu, was performed by a single observer. The sample preparation for transmission electron microscopy has been described earlier (19).

Ultrasonographic placental examination

Image-directed pulsed and colour Doppler ultrasound equipment (Acuson Sequoia 512; Acuson Corporation, Mountain View, CA, USA; Voluson Expert 730 and Voluson E8, GE Medical Systems, Kretz, Austria) with 4–8 MHz convex probes was used to obtain umbilical artery blood velocity waveforms from free loops of the umbilical cord. For the qualitative analysis of the umbilical artery blood velocity waveforms, the high-pass filter was set to a minimum, and the angle of insonation was kept at < 15 degrees. The median interval between the ultrasonographic examination and delivery was 5 days (range 0–21 days).

RESULTS

Dermatological characteristics of the 12 included pregnancies (10 women) are summarized in Table I. We have partly described patients 5 and 6 in our previous study (8).

Clinical presentation

All but 2 mothers with PG were multiparous. No PG was identified in their previous pregnancies (median 2 (range 1–3)). The majority of the mothers (58%) presented symptoms during the last trimester of pregnancy (Table I). Three mothers delivered after the index PG pregnancy, and PG developed in 2 (33%) of the 6 consecutive pregnancies. These 2 pregnancies were the only ones in this series with PG onset during the first trimester (Table I). Median postnatal follow-up was 2.0 years (range 0.5–8.7 years).

Pruritus was the principal symptom in all women. At the first dermatological visit 7 (58%) women had blistering eruptions and subsequently all but one developed blisters. There was cutaneous involvement in the abdomen and periumbilical area in all cases. Blisters were detected in the extremities, chest, back, areolas, vulva and armpits as well (Table I; see Fig. 1 for an example). Linear C3 depositions in the basement membrane zone were present in all 12 cases. IgG depositions were positive in 3 out of 12 (25%) women. Linear C3 depositions were also detected in the villous trophoblastic basement membrane zone in PG placenta (Fig. 2a), but not in normal placenta (data not shown). At the onset of PG symptoms at 8–36 gestational weeks, anti-BP180-IgG levels were approximately 4–10-fold compared with the upper limit of the normal value in all cases analysed ($n = 6$) (Table I).

Systemic corticosteroids were the mainstay treatment. Prednisolone at doses of 20–50 mg per day was used in 8 out of 12 (66%) cases. Three women (25%) were treated successfully with topical corticosteroids and antihistaminic agents only, and all patients received them in addition to systemic treatment. Cyclosporine was added to systemic corticosteroid due to severe PG manifestation in case 7. Four (33%) women continued systemic corticosteroid treatment longer than one month after the delivery. Median (range) length of systemic cortisone treatment was 2 weeks (1–10) during pregnancy and 2 months (0.5–15) postpartum. Two (17%) women reported premenstrual flare-ups, and one of them still develops skin symptoms on her feet 6 years after the delivery. Two women have used oral contraceptives and neither reported further symptoms of PG.

Prenatal testing and pregnancy outcome

Obstetric characteristics of the 12 PG pregnancies are presented in Table II. One pregnancy (8%) was complicated by preeclampsia and foetal growth below the 5th percentile (20). Three (25%) neonates were delivered prematurely at > 35 gestational weeks with a spontaneous onset of labour. Antenatal evaluations of foetal growth, biophysical profile score and Doppler ultrasonographic evaluation of placental function were normal in all cases but one: foetal growth in the 2nd

Table I. *Demographic and clinical data of patients with gestational pemphigoid*

Pat. no.	Age, years	GA at onset of symtoms	DIF findings (C3/IgG)	BP180-ELISA[a]	Sites of involvement (including blisters)	Main treatment	Subsequent pregnancy
1	35	24+	+/–	50	Abdomen, extremities	Prednisolone	
2	32	37+	+/+	NA	Abdomen, loins, forearms	Prednisolone	
3	35	35+	+/–	NA	Palms, areolas, vulva, abdomen	Topical steroids	
4	32	16+	+/–	NA	Abdomen, loins, armpits, upper arms	Topical steroids	
5	29	37+	+/–	27	Abdomen, extremities[b]	Prednisolone	One unaffected
6a	21	37+	+/–	NA	Abdomen, arms, loins	Methylprednisolone	One affected (6b)
6b	23	8+	+/–	40-67-83	Forearms, lower legs, soles; spreading	Methylprednisolone	
7	32	27+	+/+	77-110-41	Abdomen, trunk, extremities; spreading	Prednisolone, Cyclosporine	
8	32	22+	+/–	50	Abdomen, loins, extremities	Prednisolone	
9	34	36+	+/+	43	Abdomen, ankles, wrists	Topical steroids	
10a	28	32+	+/–	NA	Abdomen, palms, soles, arms	Prednisolone	One affected (10b)
10b	30	10+	+/–	NA	Feet, soles, palms	Topical steroids	3 unaffected

[a]U/ml, normal reference < 9 U/ml, first values given are at the onset of disease and latter during the course of disease. [b]No blisters.
GA: gestational age, weeks; DIF: direct immunofluorescence microscopy; NA: not available.

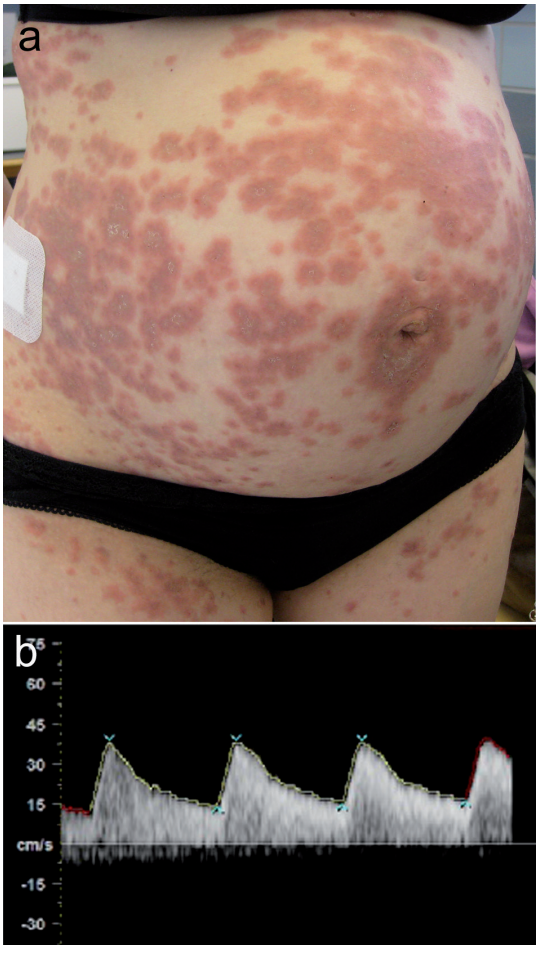

Fig. 1. (a) Urticarial papules, plaques and blisters on the abdominal skin and thighs of gestational pemphigoid case 7. (b) Normal umbilical artery blood flow profile at >35 gestational weeks.

percentile, oligohydramnion and decreased diastolic velocity in the umbilical artery as a sign of increased placental impedance was detected in the pregnancy complicated by preeclampsia and foetal growth restriction. This neonate was delivered via a Caesarean section due to foetal distress during labour. Another Caesarean section was performed due to malpresentation. Normal umbilical artery pH values at birth and 5-min Apgar scores ≥9 were detected in every case. Despite normal birth weight percentiles in all but one case, the placental-to-birth weight ratio was abnormal in half of the PG pregnancies. In 5 cases the placental-to-birth weight ratio was below the 10th percentile and in one case it was above the 90th percentile (Table II) (21). Two neonates were followed in the neonatal unit after delivery due to respiratory problems without assisted ventilation, but no significant neonatal morbidity up to the age of one month was reported.

Placental ultrastructural findings

Transmission electron microscopy revealed distinct hemidesmosomes in trophoblast basal areas in the control placentas (Fig. 2b), whereas hemidesmosomes in PG placenta were less developed (Fig. 2c). Moreover, in PG placentas basement membranes were partially detached from the trophoblasts (Fig. 2d).

DISCUSSION

According to previous studies, PG not only affects the maternal skin, but may complicate the pregnancy through miscarriage, preterm delivery, foetal growth

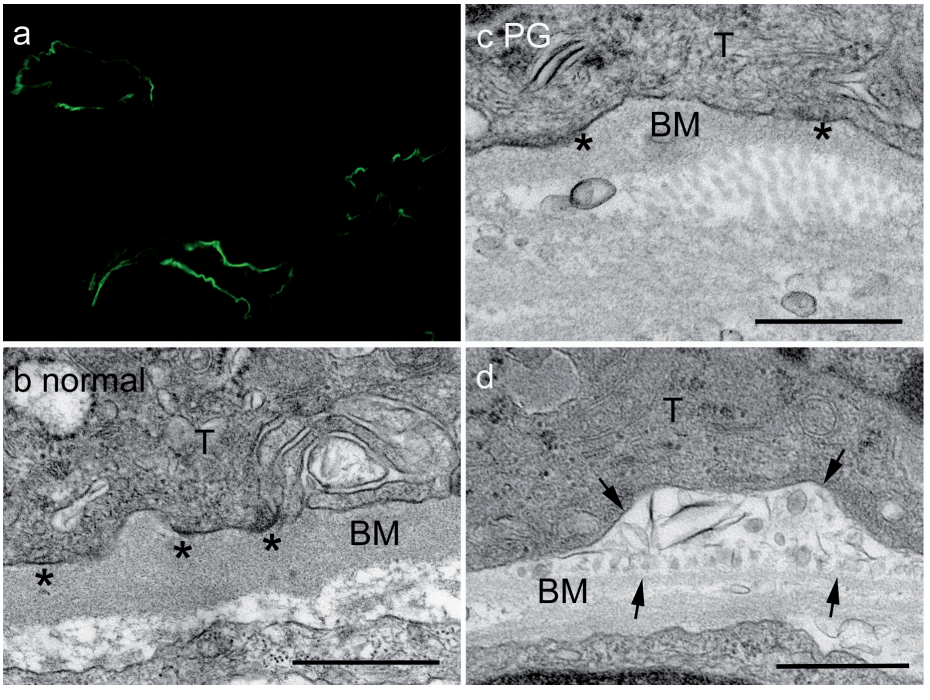

Fig. 2. (a) Direct immunofluorescence analysis of gestational pemphigoid (PG) placenta showed linear C3 positivity in the villous trophoblastic basement membrane (BM) in patient 7 (20× original magnification). (b) Transmission electron microscopy analysis of normal placenta showed well-developed hemidesmosomes (*asterisk*), but (c) in PG placenta hemidesmosomes were undeveloped. (d) In addition, partial BM microseparation (*arrows*) is observed in PG placenta. T: trophoblast; scale bars 500 nm.

Table II. *Obstetric outcomes of PG pregnancies*

Pat. No.	Gravidity	Parity	GA at onset of symtoms (week)	UA blood flow profile	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	GA at delivery (week+day)	Birth weight, g (percentile)	Placental weight, g	Placental to birth weight ratio (%)	5-min Apgar score	UA pH
1	2	1	24+	Normal	146	73	35+5	2,535 (26)	455	17.9	9	7.29
2	3	2	37+	Normal	108	56	38+6	3,470 (62)	525	15.1	9	7.23
3	3	2	35+	Normal	115	73	38+1	3,810 (91)	600	15.7	9	7.24
4	3	1	16+	Normal	116	72	39+0	3,070 (27)	535	17.4	9	7.32
5	1	0	37+	Normal	110	71	40+5	3,950 (82)	660	16.7	9	7.34
6a	2	0	37+	Decreased diastolic flow	132	88	37+5	2,290 (2)	276	12.0	8	7.25
6b	4	1	8+	Normal	121	68	35+2	2,530 (36)	243	9.6	9	7.36
7	4	2	27+	Normal	117	67	35+4	2,870 (63)	550	19.1	9	7.32
8	3	2	22+	Normal	123	61	39+5	3,360 (43)	450	17.0	9	7.32
9	4	2	36+	Normal	122	68	38+6	3,725 (81)	430	14.1	9	7.30
10a	3	2	32+	Normal	120	82	38+6	3,050 (27)	650	25.0	9	7.32
10b	4	3	10+	Normal	131	83	38+3	2,565 (6)	770	20.7	9	7.28
Median	3	2	31+	Normal	121	72	38+5	3,060	530	16.9	9	7.30
(range)	(1-4)	(0–3)	(8+–37+)		(108–141)	(56–88)	(35+2–40+5)	(2290–3950)	(243–770)	(9.6–25.0)	(8–9)	(7.23–7.36)

GA: gestational age; UA: umbilical artery.

restriction and neonatal blistering (15, 22, 23). Currently, no guidelines exist for PG pregnancy monitoring and foetal surveillance. While placental failure has been associated with this pregnancy-associated bullous dermatosis, we decided to investigate placental morphology and function as well as perinatal outcome in 12 PG pregnancies in Finland in 2002 to 2011.

In the present study, all but 2 mothers were multiparous (83%). This is in line with previous reports, although it is currently unknown why PG is more common in multiparous than primiparous women (15, 24). Ten (83%) of our patients developed PG in the second and third trimesters, which coincidences approximately with the 64% proportion in a large British multicentre clinical survey (24). In the study by Chi et al. (24), early PG onset in the first and second trimesters was associated with increased morbidity and decreased gestational age at delivery. Among our 2 patients with PG onset in the first trimester, only patient 6 demonstrated a more severe PG in her subsequent pregnancy and delivered at 35+ gestational weeks with normal neonatal outcome, while a mild skin eruption in patient 10 healed spontaneously over a few weeks. The explanation for this spontaneous remission remains unclear. Furthermore, all preterm deliveries in this series were identified among 5 mothers with PG onset prior to 26 gestational weeks, which is in line with the report by Chi et al. (24). A subsequent pregnancy with no PG has been reported to be rare, with a prevalence of 8% (25). Our high rate of unaffected subsequent pregnancies (67%) is most likely due to the small number of subsequent pregnancies. In addition, ethnic issues, which have not been addressed in previous studies, may play a role.

In all cases the first site of PG involvement was abdominal skin, and in the majority the onset was periumbilical. Frequent periumbilical involvement has been reported earlier (15), albeit Castro et al. (26) reported the extremities to be the most frequently affected site. Previously, blistering has been associated with adverse pregnancy outcome, especially decreased gestational age at delivery (24). In this series, however, the number of preterm deliveries (25%) was not higher than in earlier reports (20–34%) despite blister development in all cases but one (17, 24). In 2 pregnancies (6b and 7) skin involvement with blisters was very extensive. One of these women delivered at 35+ gestational weeks with no significant neonatal morbidity.

In the current study, none of the 3 (25%) preterm neonates who were delivered beyond > 35 gestational weeks showed any significant neonatal morbidity. During the study period, the percentage of preterm deliveries before 37+0 gestational weeks in Finland varied between 5.1% and 5.3% annually (27). This series thus confirms earlier data indicating an increased incidence of premature deliveries in PG pregnancies (15, 17, 18). In our series, one pregnancy of a smoker was complicated by

late preeclampsia and foetal growth in approximately the 2nd percentile. This is in line with the 8–14% prevalence of preeclampsia in various regions in Finland (28). We did not observe any maternal pregnancy- or non-pregnancy-associated co-morbidity, except in the case with preeclampsia.

Interestingly, the current study demonstrates abnormal placental-to-birth weight ratios in 50% of the cases, although the birth weight percentiles were normal in all but one case (Table II) (21). Recent studies suggest an association between both low and high placental-to-birth weight ratios and higher incidence of placenta-originated pregnancy complications and later cardiovascular and metabolic morbidity in adulthood (29, 30). However, currently there is no data available about the later development and morbidity of offspring born from PG pregnancies. This study design does not allow us to speculate whether abnormal placental-to-birth weight ratios are due to PG itself or its treatment with systemic corticosteroids.

Morphological data on PG placentas is rare. We and others have earlier shown that there is an accumulation of C3 complement and IgG, mild villitis, and collections of immature fibrotic villi in term PG placenta with no difference in collagen XVII expression compared with normal term placenta (8). In the present study, detachment of the basement membrane in PG placenta and undeveloped hemidesmosomes is most probably due to autoimmune reaction against placental collagen XVII, the main constituent of hemidesmosomes. Also, additional, non-inflammatory mechanisms may be involved, since sera from patients with bullous pemphigoid is shown to decrease the expression of collagen XVII in cultured keratinocytes (31, 32). Further experiments are required to investigate whether pemphigoid autoantibodies disturb collagen XVII expression also in cultured trophoblasts. In any case, we speculate that the current ultrastructural findings could explain the slight malfunction of PG placenta leading to adverse pregnancy outcomes.

Adverse foetal outcomes associated with PG are proposed to be caused by a minor placental failure induced by autoantibodies against collagen XVII (14). Umbilical artery Doppler assessment has been used to evaluate placental function in complicated pregnancies. Increased umbilical artery pulsatility, decreased diastolic velocity and absent or reversed velocity in end-diastole are the hallmarks of increased impedance and placental malfunction (33, 34). While no guidelines exist for PG monitoring, the mothers in this study were referred to their obstetricians, who made individual follow-up schedules for them. Normal umbilical artery Doppler recordings in all except one case and normal neonatal outcome suggest that currently available monitoring methods do not detect possible placental malfunction caused by morphological PG changes. Vascular sprouting of the placental villous tree mainly occurs before mid-gestation (35), and PG changes possibly occurring not until late in the second and third trimester might thus not have a huge impact on placental function. In the single case report with umbilical artery Doppler ultrasound follow-up in PG, abnormal placental function was detected in a PG pregnancy complicated by foetal growth restriction (36). Our placental functional data and good neonatal outcome in this study suggest, however, that clinically detectable placental malfunction related to PG is rare. Furthermore, systemic steroid medication for up to 10 weeks during pregnancy did not seem to affect the neonatal outcome.

In clinical practice, vaginal ultrasound evaluation of cervical length and possible opening of the internal cervical os are the gold standards in the prediction of possible preterm delivery (37). In this series, digital cervical examination was normal 5–20 days prior to preterm delivery. Although prediction of preterm delivery is difficult, we propose that, due to an increased incidence of preterm deliveries in PG pregnancies, obstetric follow-up with vaginal ultrasound assessment of cervical length is indicated. Our results also suggest that mothers can be reassured that good perinatal and neonatal outcome with normal birth weight, pH-values, Apgar scores and low neonatal morbidity can be expected.

The sample size of 12 pregnancies naturally limits the interpretation of our results. However, the median birth rate in Finland during the study period was approximately 58,000 per year, and we therefore assume that we were able to recruit nearly all PG patients during 2002 to 2011, as the estimated PG incidence is approximately 1:50,000 (1). Naturally, a strict obstetric follow-up protocol and a higher number of placentas available for morphological analysis would have enhanced our findings.

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The authors declare no conflicts of interest.

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