Retrospective evidence on outcomes and experiences of pregnancy and childbirth in epidermolysis bullosa in Australia and New Zealand

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A R T I C L E   I N F O
Article history:
Received 24 November 2014
Received in revised form 14 December 2014
Accepted 15 December 2014

Keywords:
Epidermolysis Bullosa
Pregnancy
Childbirth
Anesthesia

A B S T R A C T
Background: Pregnancy in epidermolysis bullosa (EB) has not been comprehensively studied.
Objective: We aimed to develop a foundational database, which could provide peri-obstetric advice in EB.
Methods: Survey questionnaires were sent to obstetricians, unaffected mothers of EB babies, and mothers with EB. Results were analyzed using chi-square, Fisher exact, and t-tests.
Results: Out of 1346 obstetricians surveyed, 195 responded, and only 14 had encountered EB. All recommended normal vaginal delivery (NVD), except for one elective Caesarean section (CS). We received responses from 75 unaffected mothers who had delivered EB babies. They had significantly more complications in their EB pregnancies compared to their non-EB pregnancies. A further 44 women with various types of EB who had given birth responded. Most delivered via NVD and had no significant increase in complications in both their EB and non-EB pregnancies. In both groups, there were no significant differences in blistering at birth in babies delivered via NVD and CS.
Conclusion: In conclusion, most patients with EB who are capable of giving birth do not have an increased risk for pregnancy-related complications and NVD appears to be safe. Awareness of this data amongst obstetricians and dermatologists should lead to improved quality of care for mothers and babies affected with EB.

Introduc tion
Ongoing research on various aspects of epidermolysis bullosa (EB) is currently underway. Most reports are focused on the molecular basis and classification of this disease. Diagnostic criteria and treatment options for this condition are constantly evolving, but little focus has been directed towards pregnancy and childbirth in these patients. There is a scarcity of literature available addressing this important issue, and this paper aims to fill that gap, and provide sound evidence and guidance for mothers who are pregnant with EB babies.

Milder forms of EB, such as EB simplex, often go undiagnosed: this could explain the relative lack of pregnancy cases reported. On the other hand, very few reports in the literature detail pregnancy and childbirth experiences of mothers and infants with more severe forms of EB, including junctional EB (JEB) and recessive dystrophic EB (RDEB). It does not always follow that all patients with severe forms of EB will have difficult pregnancies. The bulk of the available literature is mainly on prenatal diagnosis of severe forms of EB (JEB or JEB with pyloric atresia, Herlitz JEB, and RDEB) and its role in management decisions such as termination. A survey performed in Denmark amongst obstetricians and pediatricians showed that in the case of newborns with severe EB, there was a strong consensus to withhold life-prolonging treatment, reflecting attitudes to EB.

A patient with non-Herlitz JEB was reported who had two miscarriages prior to giving birth successfully via Cesarean section under epidural anesthesia. A patient with RDEB in Germany had two vaginal deliveries resulting in healthy babies, with uncomplicated episiotomy wound healing, and no exacerbations of EB during her...
pregnancy (Büscher et al., 1997). Another patient with RDEB had preterm labor at 36 weeks and premature rupture of membranes, yet delivered a healthy baby via Cesarean section (Bianca et al., 2003). In the French literature, there is a report of a patient with EBS who developed a herpetiform flare of EBS-DM during the first two months of her pregnancy (Diris et al., 2003). More recent reports include that of a patient with Kindler syndrome with vaginal stenosis who had a successful Cesarean delivery (Hayashi et al., 2007). The report most recently published is a case report of 11 pregnancies in three patients with recessive EB in Australia. One of the patients had non-Herlitz JEB and had delivered two unaffected babies via NVD eight years apart. The two other patients were sisters who both had generalized RDEB. One of them delivered three healthy unaffected babies via NVD, and the other delivered five unaffected babies via NVD. They all had no complications or flare of their EB during their pregnancies and the peripartum period (Choi et al., 2011). More recently, there has been a report of three more women, each with RDEB-intermediate (RDEB-I), all of whom had successful vaginal deliveries without major cutaneous or mucosal complications (Hanafusa et al., 2012). There is also an online patient information handout on pregnancy and childbirth in EB published by the Dystrophic EB Research Association (DEBRA) UK group in May 2006 which reports that women with EB have successfully had vaginal and Cesarean deliveries (Pillay, 2006).

Labor and delivery practices include airway management strategies, the role of regional anesthesia, and the use of nonadhesive tape and padding (i.e. Mepitel, Mepitex, Mepitac, Mepiform) as minor trauma may lead to severe lesions (Price and Katz, 1988; Pillay, 2006). Regional anesthesia has been used successfully in these patients. There are five reported cases that used either spinal or epidural anesthesia for Cesarean section, and epidural anesthesia for vaginal delivery without any ensuing complications (Baloch et al., 2008; Broster et al., 1987; Berryhill et al., 1978).

In view of this limited information, we designed a survey looking at the experiences of a large group of obstetricians, unaffected mothers who delivered babies with EB, and EB patients themselves who have delivered babies. We have developed a foundational database, and have developed recommendations on obstetric advice in relation to EB.

Methods

This study was granted ethics approval by the South Eastern Sydney Local Health District Human Research Ethics Committee - Southern Sector on the 3rd of October, 2006 until July, 2012.

Questionnaires were sent out to three participant groups, namely obstetricians in Australia, unaffected mothers who had given birth to EB babies, and EB females who had given birth.

The list of obstetricians was obtained from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), whilst the list of EB patients and their parents was obtained from patients known to us, most of whom are in the Australasian EB Registry which is being maintained at St. George Hospital, Sydney, NSW, Australia (Kho et al., 2010). The appropriate questionnaires were mailed to these obstetricians and patients in the post with self-addressed envelopes. Some questionnaires were also handed out to member families of DEBRA Australia and New Zealand, new patient referrals seen at St. George Hospital, and patients attending EB clinics. All participants had given signed informed consents to participate in the study and share their data.

A substudy was also performed that looked into the percentage and locations of blisters, if any, in babies born with EB to unaffected mothers and those diagnosed with EB This was achieved by sending out further questionnaires with body maps to both groups of respondents.

The data was then collated and summarized over a period of 4.8 years (October 2006–August 2011). Statistical analysis was performed using chi-square tests, t-tests, and Fisher exact tests. The statistical program used was SigmaStat. Based on the results, peri-obstetric recommendations were made for EB patients and mothers giving birth to EB babies.
the baby’s head. The third case was a baby with JEB delivered via NVD and forceps, which resulted in skin erosion from the baby’s face. The fourth case was a baby with JEB delivered via NVD and vacuum suction resulting in skin being eroded from the baby’s feet. The fifth case was a baby with JEB delivered via emergency CS using both vacuum suction and forceps, resulting in facial erosions and hematomas. The overall rate of emergency CS was 8% but for pregnancies with JEB offspring it was 21%, suggesting that labor in this group is more complicated. Out of the 84 babies with EB, 46 (55%) had blisters at birth, most commonly in the severe types of EB (JEB and RDEB) and the others (45%) developed blistering in the days or weeks subsequently.

Most mothers surveyed were unaware that they were going to deliver a baby with EB. Some expressed the view that their obstetrician could have given more accurate information regarding the genetics and severity of the EB type that affected their babies. Other mothers, particularly with children affected by severe EB types recommended prenatal screening and informed decisions about termination options. Those whose babies had blistering due to birth trauma thought to be associated with vaginal delivery recommended delivery via CS.

**Group 3: Mothers with EB who had given birth**

Out of 55 females with EB of childbearing age surveyed, 44/55 (80%) returned completed questionnaires. We tried to contact all 11 non-responders, and sent out new surveys forms. Three were returned unanswered due to change of addresses. The revised response rate of 44/55 or 85% of contactable female EB patients of childbearing age was very high. For those known to have at least one child also affected with EB (32/36), the response rate was 89%. We received responses was very high. For those known to have at least one child also affected with EB (32/36), the response rate was 89%. We received responses.

Table II

| Mode of Delivery | Babies born with EB | Unaffected |
|------------------|---------------------|-----------|
|                  | EBS | JEB | DDEB | RDEB | Total EB1 |
| NVD              | 26  | 11  | 17   | 13   | 67 (80%) |
| PCS              | 7   | 0   | 1    | 2    | 10 (12%) |
| ECS              | 2 (6%) | 3 (21%) | 1 (5%) | 1 (6%) | 7 (8%) |
| Total            | 35  | 14  | 19   | 16   | 84         |

EB, epidermolysis bullosa; NVD, normal vaginal delivery; PCS, Planned Cesarean Section; ECS, emergency Cesarean section.

1 Percentages of actual deliveries in parentheses.

**Table III**

| Complications                          | Unaffected babies (n = 90) | NVD | PCS | ECS |
|----------------------------------------|----------------------------|-----|-----|-----|
| Bleeding                               | 0                          | 0   | 0   | 1   |
| Cord coil around neck                  | 0                          | 0   | 0   | 1   |
| Emergency CS for cephalopelvic disproport | 1                          | 0   | 1   | 0   |
| Emergency CS for other reasons         | 4                          | 0   | 4   | 2   |
| Gestational diabetes                   | 1                          | 1   | 0   | 4   |
| Hypertension                           | 0                          | 0   | 0   | 3   |
| Hypertension                           | 1                          | 0   | 1   | 0   |
| Hypoglycaemia                          | 1                          | 1   | 0   | 0   |
| IUGR                                    | 0                          | 0   | 0   | 2   |
| Oligohydramnios                        | 0                          | 0   | 0   | 1   |
| Placenta previa                        | 0                          | 0   | 0   | 2   |
| Polyhydramnios                         | 1                          | 0   | 1   | 0   |
| Preeclampsia                           | 1                          | 1   | 0   | 3   |
| Preterm labour                         | 1                          | 1   | 0   | 2   |
| PUPPP2                                 | 0                          | 0   | 0   | 1   |
| Total                                  | 11 (12%)1                  | 22 (26%) |

EB, epidermolysis bullosa; PCS, Planned Cesarean Section; ECS, Elective Cesarean Section.; IUGR, intrauterine growth retardation; PUPPP, pruritic urticarial papules and plaques of pregnancy.

1 p = .03
NVD versus CS
RDEB babies delivered via NVD and planned CS. Overall, there was no
tinction, there were no signi
ificant blistering at birth in RDEB babies is signi
ficant differences in blistering at birth in all EB babies delivered via NVD versus CS,
p = .012 and
s exact test showed that blistering in JEB and RDEB babies
p = .769). Fisher
p = .016 and
b .001 respec-
tively). Blistering in DDEB babies was not significantly greater than blister-
ing in babies with EBS (p = .769). Fisher’s exact test showed blis-
tering at birth in RDEB babies is significantly more common than in
DDEB babies (p = .012). Finally, blistering in JEB babies was not sig-
ificantly different from blistering in RDEB babies (p = .315). In addi-
tion, there were no significant differences (p = .121) in blistering of
RDEB babies delivered via NVD and planned CS. Overall, there was no
significant difference in blistering at birth in all EB babies delivered via
NVD versus CS (p = .136).

Table VI
Proportions of EB babies born with blisters at birth in relation to their mode of delivery.

| Type of EB | Blisters at birth | NVD | PCS | ECS |
|-----------|-------------------|-----|-----|-----|
| EBS       | 20/49 (41%)       | 4/7 (57%) | 2/5 (40%) |
| JEB       | 11/14 (79%)       | 8/11 (73%) | 0/0 (0%) | 3/3 (100%) |
| DDEB      | 11/24 (46%)       | 9/21 (43%) | 1/0 (100%) | 2/2 (100%) |
| RDEB      | 15/16 (94%)       | 2/2 (100%) | 1/1 (100%) |
| Total     | 57/103 (55%)      | 43/82 (52%) | 6/10 (60%) | 8/11 (73%) |

ED, epidermolysis bullosa; PCS, planned Caesarean section; ECS, elective Caesarean section; CS, Caesarean section.

Discussion
An international expert consensus on delivery recommendations for patients with EB or for EB-unaffected mothers expecting infants with EB has yet to be established. Hence, this survey is quite timely. Due to the rarity of this family of diseases, there was a relatively low response rate amongst obstetricians, most of whom felt that NVD should be the recommended mode of delivery for EB patients giving birth. Data from a larger prospective cohort study within the 2005 WHO global survey on maternal and perinatal health have shown that, overall, maternal morbidity and mortality were higher in the elective CS group (5.5%) than the NVD group (1.8%). Furthermore, increased risk in NVD relates to maternal socio-demographic characteristics such as being single, young with a low level of education, gravidity, and primiparity. Increased risk for maternal morbidity and mortality in the CS group related to women with previous complications in their pregnancies or perinatal outcomes (Villar et al., 2007). This supports our data that NVD is still the recommended mode of delivery for most mothers carrying EB babies and for pregnant EB females. Despite this recommendation, there seems to be a growing preference for elective delivery by CS, particularly in Western countries.

In a recent structured survey performed to determine personal preferences of delivery method amongst obstetricians from Australia and New Zealand (which had a 26% response rate), 11% of obstetricians chose elective CS in the absence of any clinical indication. Elective CS procedures were also the preferred method of child-birth in cases of predicted fecal incontinence (83.5%), urinary incontinence (81.5%), perineal damage (68.5%), and fear of damage to the baby (24%) (Land et al., 2001).

The rates of CS in most developed countries are quite similar, with 23.3% of all births in Australia, 21.3% in the UK and 26% in the US (Dodd et al., 2007) performed by CS. Overall, NVD is still the most recommended mode of delivery worldwide and appears to be the safer method of childbirth. It should be emphasized, however, that forceps delivery or vacuum suction should be avoided during NVD or CS, as our data have shown that babies with severe forms of EB had severe erosions on their head and feet. The data also suggest that Cesarean wounds heal well in mothers with EB, and that care during breastfeeding (i.e. use of nipple shield) or bottle-feeding, are recommended options if blistering is severe.

As for applicability of data derived from the mothers of children with EB, our response rate of 75% from mothers of children with EB is significant, given that the average response rate cited in the literature for mailed physician questionnaires is around 61% and this has remained quite stable over time (Cummings et al., 2001); Hence, the results of our data collection should have excellent applicability. Interestingly, the surveys of mothers who gave birth to babies with EB reveals that there were significantly more complications in deliveries by CS
compared to the majority who delivered via NVD. This was particularly true for infants with JEB or RDEB. Overall, either of the two modes of delivery seemed to be comparable for blistering rates. Blistering at birth in the different types of EB showed the more severe forms of EB (JEB and RDEB) had significantly more blistering than the milder EBS and DDEB forms, as might be expected. Together, this suggests that if it were known in advance that a mother was pregnant with a baby with EB, delivery via NVD would still be recommended as the preferred mode of delivery as long as it is safe to do so; for example, providing that cephalopelvic disproportion is not a problem. This would be the case for 50% of mothers with a dominant form of EB such as EBS and DDEB. It would be more difficult, if not impossible, to predict complications in those with no known family history of a recessive form of EB. Genetic counseling and discussion of prenatal diagnostic options are recommended for all EB patients when contemplating pregnancy (Sybert, 2010; Fasshi and McGrath, 2010).

Conclusions

Most patients with EB are capable of giving birth without increased risk of pregnancy-related complications. Unaffected mothers who have given birth to children with EB have had relatively normal pregnancies comparable to previous pregnancies yielding unaffected children. However, when a mother is known to be carrying an EB pregnancy, delivery via normal vaginal delivery is no more likely to result in complications and blisters at birth in the EB-aFFECTed newborn. Hence, there appears to be no justification in performing a Cesarean section to reduce complications for the mother with EB nor the infant with EB in order to avoid EB-related complications. CS should be reserved for the traditional indications of all pregnant mothers. Lastly, awareness of these data amongst obstetricians and dermatologists should lead to informed advice and improved quality of care for both EB mothers and EB babies alike.

Recommendations for expectant patients with EB

1. Normal vaginal delivery with regional anesthesia is generally safe, and episiotomy may reduce perineal tears.
2. Vacuum suction or forceps delivery is not recommended in mothers delivering babies with EB or where the EB status of the baby is unknown.
3. In mothers expecting to deliver a baby with EB, normal vaginal delivery is still the preferred mode of delivery.
4. Only non-adhesive tape and dressings are to be used during anesthesia and surgery.

References

Baloch MS, Fitzwilliams B, Mellerio J, Lakasing L, Bewley S, O’Sullivan G. Anesthetic management of two different modes of delivery in patients with dystrophic epidermolysis bullosa. Int J Obstet Anesth 2008;17:153–8.
Berryhill RE, Benumom JL, Saidman LJ, Smith PC, Plumer MH. Anesthetic management of emergency cesarean section in a patient with epidermolysis bullosa dystrophica polydactyloplactica. Anesth Analg 1978;57:281–3.
Bianca S, Reale A, Ettore G. Pregnancy and caesarean delivery in a patient with dystrophic epidermolysis bullosa. Eur J Obstet Gynaecol Reprod Biol 2003;110:235–6.
Broster T, Plaeck R, Eggers JP. GWN. Epidermolysis bullosa: anesthetic management for cesarean section. Anesth Analg 1987;66:341–3.
Buscher U, Wessel J, Anton-Lamprecht I, Dudenhausen JW. Pregnancy and delivery in a patient with mutilating dystrophic epidermolysis bullosa (Halleux-Siemens type). Obstet Gynecol 1997;89:817–20.
Choi SD, Kho YC, Rhodes LM, Davis GK, Chapman MG, Murrell DF. Outcomes of 11 pregnancies in three patients with recessive forms of epidermolysis bullosa. Br J Dermatol 2011;165:700–1.
Cummings SM, Savitz LA, Konrad TR. Reported response rates to mailed physician questionnaires. Health Serv Res 2001;35:1347–55.
D’Alessio M, Zambruno G, Charlesworth A, Lacour JP, Meneguzzi G. Immunofluorescence analysis of villous trophoblasts: a tool for prenatal diagnosis of inherited epidermolysis bullosa with pyloric atresia. J Invest Dermatol 2008;128:2815–9.
Döris N, Boraletti F, Lepreaux S, Talcab A, Léauté-Labrèze C. Herpetic-like worsening of an epidermolysis bullosa simplex during pregnancy. Article in French. Ann Dermatol Venereol 2003;130:769–72.
Dodd JM, Crowther CA, Hiller JE, Haslam RR, Robinson JS. Birth after caesarean study - planned vaginal birth or elective repeat caesarean for women at term with a single previous caesarean birth: protocol for a patient preference study and randomized trial. BMC Pregnancy Childbirth 2007;7:17.
Fasihri H, McGrath JA. Prenatal diagnosis of epidermolysis bullosa. Dermatol Clin 2010;28:231–8.
Hanafusa T, Tanai K, Umegaki N, Yamaguchi Y, Fukuda S, Nishikawa Y, et al. The course of pregnancy and childbirth in three mothers with recessive dystrophic epidermolysis bullosa. Clin Exp Dermatol 2012;37:30–4.
Hayashi S, Shimoita S, Itami S, Murata Y. Pregnancy and delivery with Kindler syndrome. Gynecol Obstet Invest 2007;64:72–4.
Kho YC, Agero AL, Rhodes LM, Robertson S, Su J, Varigos G, et al. Epidemiology of EB in the Antipodes: the Australasian EB Registry with a focus on Herlitz Junctional EB. Arch Dermatol 2010;146:635–60.
Land R, Parry E, Rane A, Wilson D. Personal preferences of obstetricians towards childbirth. Aust N Z J Obstet Gynaecol 2001;41:249–52.
Marinkovich MP, Meneguzzi G, Burgeson RE, Blanchet-Bardon C, Holbrook KA, Smith LT, et al. Prenatal diagnosis of Herlitz junctional epidermolysis bullosa by amniocentesis. Prenat Diagn 1995;15:1027–34.
Norup M. Treatment of severely diseased newborns: a survey of attitudes among Danish physicians. Acta Pediatr 1999;88:438–44.
Pfendner EG, Nakano A, Pukkinnen L, Christiano AM, Uitto J. Prenatal diagnosis for epidermolysis bullosa: a study of 144 consecutive pregnancies at risk. Prenat Diagn 2003;23:447–56.
Pillay E. Care of the woman with EB during pregnancy and childbirth [Internet]. cited 2014 November 4, UK:DebRA. Available from: http://www.debra.org.uk/downloads/community-support/care-of-a-woman-with-eb-during-pregnancy.pdf; 2006.
Price T, Katz VL. Obstetrical concerns of epidermolysis bullosa. Obstet Gynecol Surv 1988;43:445–9.
Sybert VP. Genetic counselling in epidermolysis bullosa. Dermatol Clin 2010;28:239–45.
Villar J, Carroli G, Zavaleta N, Donner A, Wojdyla D, Faundes A, et al. World Health Organization 2005 Global Survey on Maternal and Perinatal Health Research Group. Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study. BMJ 2007;335:1025.
Yan EC, Ahtuvalia J, Lane AT, Bruckner AL. Treatment decision-making for patients with the Herlitz subtype of junctional epidermolysis bullosa. J Perinatol 2007;27:307–11.