A review of the obstetric management of patients with epidermolysis bullosa

L A Bolt BSc*, **G O'Sullivan** MD FRCA†, **D Rajasingham** MBBS MRCOG* and **A Shennan** MD FRCOG*

*Maternal and Fetal Research Unit, King's College London, Division of Reproduction and Endocrinology, St Thomas' Hospital, London, UK;

†Departments of Obstetric Anaesthesia, St Thomas' Hospital, London, UK

Summary: Epidermolysis bullosa (EB) is a rare inherited skin condition characterized by the development of blisters after minor mechanical friction or trauma. There are few reported pregnancies in the literature in these women. We describe a pregnancy we recently managed. The collated series of pregnancies show that there are no additional antenatal or postnatal problems and that the skin itself does not worsen during pregnancy. Vaginal delivery is most favourable, but if a caesarean section is required, regional anaesthesia should be attempted. A multidisciplinary team should be active throughout the pregnancy of these women and a well-documented labour plan should be made in advance.

Keywords: complications, general medicine, epidermolysis bullosa, management

CASE STUDY

A 25-year-old, 53 kg, 149 cm (BMI body mass index 23.9 kg/m²) patient with severe recessive dystrophic epidermolysis bullosa (RDEB) presented to the obstetric services at St Thomas' Hospital at 15⁺² weeks gestation. This was her second pregnancy after having had a miscarriage at 6⁺⁰ weeks nine months earlier. The patient was severely affected by RDEB with limited mouth opening, extensive blistering of the back, chest and hands and very poor neck movement due to scarring. She was fed through a percutaneous endoscopic gastrostomy due to severe oesophageal stenosis which resulted in chronic anaemia. She also had iatrogenic Addison's disease as a result of long-term corticosteroid cream use.

Owing to the complexity of her condition and the lack of knowledge on the obstetric management of these patients, advice regarding the delivery method was obtained from her dermatologist, obstetrician and the obstetric anaesthetist. The anaesthetist expressed concern that a general anaesthesia would pose significant risks because of limited neck rotation and extension, poorly palpable cricothyroid membrane and very limited mouth-opening precluding direct laryngoscopy or laryngeal mask insertion. Spinal anaesthesia also posed risks in this patient because of extensive bullae formation on the back. It was agreed early on in the pregnancy that a vaginal delivery would be the safest option. However, the patient was extremely anxious about a vaginal delivery and an elective lower segment caesarean section (LSCS) was agreed on due to the uncertain risks/benefits of an operative mode of delivery.

During ongoing antenatal monitoring, it was noted that at 17⁺⁴ weeks gestation, her haemoglobin level had dropped to 6.8 g/dL. As a result, a blood transfusion was given bringing the haemoglobin level back to her prepregnancy level (8–10 g/dL). At 36⁺⁴ weeks gestation, an infected blister on the patient's back tested positive for methicillin-resistant *Staphylococcus aureus* (MRSA). This had a significant impact on the proposed method of delivery. Spinal anaesthesia is usually contra-indicated in patients with sepsis at the site of needle puncture; however, in this case it was thought to pose a lower risk than a general anaesthesia. The increased risk of developing bacterial meningitis from a spinal anaesthesia with the known MRSA infection in this area was extensively explained to the patient, but her preference was to avoid vaginal delivery.

At 38⁺² weeks gestation, the fetal presentation was oblique, precluding vaginal delivery. A single-shot spinal anaesthesia was given in the sitting position. Four per cent lignocaine spray was used on the skin overlying the L3/L4 intervertebral space. Two per cent lignocaine was administered via a 25-gauge needle producing a T2 sensory block. All clinicians covered gloves with 50–50 paraffin cream prior to touching the patient and avoided inducing pressure or friction on the skin. Surgical and monitoring equipment that came into contact with the patient was well padded or lubricated. The patient did not require any analgesia throughout the delivery. A healthy male infant was delivered weighing 2630 g, with Apgar scores of 9 and 10 at one and five minutes, respectively. There was an estimated 450 mL of blood loss.

Incision clips were removed five days postoperatively. The scar healed well with only slight skin sloughing around it. The patient was able to breast feed despite small blisters forming on both nipples. Both mother and baby are doing well.

Correspondence to: Lauren Bolt
Email: lauren.bolt@kcl.ac.uk

EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa (EB) is a group of rare inherited skin conditions in which there is an increased tendency to develop blisters after minor mechanical friction or trauma. The effects of EB can range from death in early infancy to increasing disability throughout life. EB affects an estimated one out of 50,000 births worldwide, irrespective of race, ethnicity or sex. The subtypes of EB are defined by the levels in the skin at which blistering occurs. This review article summarizes the difficulties of managing such women in pregnancy, labour and the postnatal period, and collates eight pregnancies reported in the literature and one additional pregnancy.

There are four main types of EB – simplex, junctional, dystrophic and Kindler syndrome – which vary in severity of skin involvement. EB simplex is the most common type of EB characterized by blistering in the intraepidermal level of the skin. Blistering usually occurs in places that experience most friction and exacerbates with increasing temperatures. Permanent scarring is often minimal in EB simplex and the lifespan of the patient is often near normal. Junctional EB is an autosomal recessive type of EB, which causes the lamina lucida level of skin to be affected by blisters. It has two major forms: the Herlitz type is often lethal during early infancy, whereas those with the non-Herlitz type often have a near-normal life expectancy. These patients often have large blisters, areas of granulation tissue and atrophic scarring. There is often more extensive and prominent respiratory, gastrointestinal and genitourinary tract involvement, resulting in the severe manifestations of this type of EB. Dystrophic EB results from abnormal production of collagen VII resulting in fragility, blistering and scarring of the skin and other epithelial surfaces. Autosomal dominant dystrophic EB has a less severe presentation with blisters mainly affecting the friction sites. Recessive dystrophic EB often results in a severely affected phenotype with widespread blisters that are slow to heal. There is characteristic atrophic scarring which can eventually lead to nail loss, pseudosyndactyly and flexural contractures of the wrist, elbow, knee and ankle joints. The teeth, mouth and oesophagus are often affected resulting in the malformation of the teeth, microstomia and oesophageal strictures.¹ The resulting difficulty in mastication and swallowing leads to malnutrition, anaemia, growth delay and weight loss.² Kindler syndrome is an autosomal recessive disorder that first manifests in infancy with acral blistering and photosensitivity.³ Over time the condition improves, but poikiloderma, nail dystrophy, and oesophageal, urethral, vaginal and anal stenosis often develop later in life.³

There are few reports in the literature of patients with EB becoming pregnant. There may be numerous reasons for the small number of obstetric patients, but most likely are the reduced lifespan and the extensive disability that EB predisposes to. There is little published literature to guide obstetricians who may therefore be very cautious when caring for a woman with EB. The first reported pregnancy in the literature occurred in 1978.⁴ Since this time there have been only seven further pregnancies^{4–8} that have been reported in the literature as shown in Table 1. We have included a ninth pregnancy recently managed at St Thomas' Hospital, London.

The few pregnancies highlight the fact that pregnancy in patients with EB is relatively rare. It is thought that patients may not be aware that they are able to have children or even sexual intercourse.⁵ Blistering around the urogenital area can

be extremely painful and problematic during sexual intercourse for these patients. Anxiety surrounding the health of the patient during the pregnancy and delivery, as well as for the health of the future children, may also be a key factor for the low pregnancy rate in this population.⁵

Antenatal care

The published pregnancies demonstrate that close antenatal monitoring of the obstetric women with EB is often practised. A multidisciplinary team including the midwife, dermatologist, obstetrician and anaesthetist should be active throughout the pregnancy. Despite the often intensive antenatal monitoring, it is thought that pregnancy itself does not affect the underlying skin condition,^{5,7} and this is confirmed in our collated series (Table 1). In addition, the reported pregnancies appear to suggest that patients with EB do not have additional non-dermatological antenatal complications compared with the general population. The one pregnancy out of nine complicated by pre-eclampsia is proportional to the rates of about 15% in the general obstetric UK population.⁹ Antenatal blood pressure monitoring should be continued with well-padded blood pressure cuffs. Cardiotocography should only be used if clinically indicated as it poses a high risk of blistering.

'Pregnancy 5' (Table 1) was complicated by mild anaemia, polyhydramnios and gestational diabetes. The mild anaemia was likely to be due to poor nutritional intake of this woman as she had developed an oesophageal stenosis prior to the pregnancy as a complication of EB.⁷ This highlights the need to promote and ensure adequate nutritional intake in those women considering having a child.

It was thought that the development of gestational diabetes in this woman caused polyhydramnios. Current literature does not suggest that EB increases the risk of developing diabetes throughout the lifespan. It seems reasonable to assume that pregnant women with EB therefore are not at an increased risk of developing gestational diabetes. It has been suggested that renal function is closely monitored throughout pregnancy, especially in those women with the dystrophic EB type where exacerbations can lead to significant renal impairment (for example, renal failure or nephrotic syndrome), which could result in the loss of the fetus if not detected early.⁷

Labour

The main complications that can arise during pregnancy in these patients are at the time of delivery. The risks and benefits of the mode of delivery and the choice of anaesthesia need to be weighed up. However, information on these two decisions is limited.⁵ It is thought that vaginal delivery should be the first choice,⁷ but this method is not completely complication-free. Vaginal delivery may be associated with vaginal mucosa blistering, sloughing of the cervical and perineal epithelium and damage to the soft tissues of the pelvic floor. In addition, blistering of the lower back, buttocks and elbows may occur during prolonged vaginal delivery. If the need for instrumental delivery is indicated, this may further increase the risk of blistering and scarring.⁵ Patients who have significant preceding vaginal or perineal involvement may be more inclined to opt for delivery by caesarean section. There have been three reported pregnancies^{5,7} with vaginal deliveries, of which one was complicated by a small posterior vaginal wall tear (Table 1).

Table 1 Pregnancies reported in the literature in patients with EB

Pregnancy	Year	Age	Type of EB (severity)	Gravida	Antenatal complications	Gestation at delivery	Mode of delivery	Anaesthesia	Indications for mode of delivery	Skin involvement	Clinical complications	Breast feeding
1. Berryhill et al. ⁴	1978	35	Dystrophic (severe)	Unknown	Pre-eclampsia	34 + 6	Emergency LSCS	General	SRM, breech presentation	Spinal + epidural anaesthesia were contraindicated due to infected lumbosacral blisters	10 min postpartum – grand mal seizure	Unknown
2. Broster et al. ⁶	1987	30	Simplex (mild)	Prima	None	38 + 0	Elective LSCS	Spinal	Previous repair of bifid uterus	None	None	Yes but small bullae developed around nipples
3. Broster et al. ⁶	1987	17	Dominant dystrophic (moderate)	Prima	None	40 + 0	Elective LSCS	Epidural	Primary cephalopelvic disproportion	None	None	Unknown
4. Buscher et al. ⁷	1997	24	Recessive dystrophic (severe)	Prima	None	40 + 4	Vaginal (induced)	None		Mediolateral episiotomy – well healed	None	Discontinued after bilateral blister formation at nipples
5. Buscher et al. ⁷	1997	24	Recessive dystrophic (severe)	Second pregnancy	Mild anaemia, polyhydramnios gestational diabetes	40 + 4	Vaginal (induced)	None		Mediolateral episiotomy – well healed	None	Unknown
6. Bianca et al. ⁸	2003	?	Recessive dystrophic (severe)	Prima	None	36 + 0	Emergency LSCS	Epidural	Genital mucous lesions, fetal growth restriction, PROM	Blister around caesarean scar	None	Unknown
7. Baloch et al. ⁵	2008	29	Recessive dystrophic (mild)	Prima	None	40 + 0	Vaginal	None		Small posterior vaginal wall tear	None	Yes without complications
8. Baloch et al. ⁵	2008	33	Recessive dystrophic (moderate)	Prima	None	39 + 1	Elective LSCS	Spinal	Patient's request	None	None	Discontinued after bilateral blister formation at nipples
9. Previously unpublished	2009	25	Recessive dystrophic (severe)	Second pregnancy	Anaemia, MRSA infected lumbosacral blisters	38 + 2	Elective LSCS	Spinal	Patient's choice	Risks of general anaesthesia deemed greater than spinal at infected site. Few blisters at LSCS scar	None	Yes but small bullae developed around nipples

LSCS = lower segment caesarean section; MRSA = methicillin-resistant *Staphylococcus aureus*; PROM = premature rupture of membranes; SRM = spontaneous rupture of membranes

Although limited by the number of reported pregnancies, this suggests there is a relatively small complication rate of vaginal deliveries and is consistent with deliveries in healthy women.

The obvious complications arising as a result of a caesarean section involve blistering and scarring of the site of excision as seen in two pregnancies in Table 1. However, the most important clinical decision in this mode of delivery in patients with EB is the choice of anaesthesia.

Any surgical procedure on a patient with EB provides challenges for the experienced anaesthetist. An extensive pre-assessment, involving ascertaining the extent of bullae, noting any systemic manifestations such as dehydration, malnutrition or anaemia,¹⁰ and airway evaluation,¹¹ must be undertaken prior to any surgery on patients with EB. Previous anaesthetic notes are invaluable in these patients.

General anaesthesia

If a number of precautions are adhered to, then general anaesthesia is reported to have a low complication rate in patients with EB.¹² There is controversy, however, as to whether general anaesthesia for surgery in these patients should be by inhalational induction or intravenous induction. Induction by inhalational agents is often more popular because of the difficulties faced with venous access.¹² However, bullae formation can occur at the site of contact with the face mask and under the chin caused by the supporting fingers during induction.¹³

General anaesthesia can also be particularly difficult in these patients because of the difficulties faced with intubation. Microstomia, poor dentition and oesophageal strictures render intubation a difficult procedure, where optimal care must be taken throughout.¹⁴ The lips, airways and laryngoscope blade should be well lubricated with soft paraffin jelly throughout the surgery,⁵ as facial, oropharyngeal and oesophageal bullae formation are increased with this technique.¹⁵ If a laryngeal mask airway is to be used, it should be well lubricated with a water-based gel and a smaller size than usual should be selected.^{5,12} Additionally, to decrease bullae formation, the cuff does not need to be fully inflated, only enough to maintain the shape.¹⁶ Vaseline gauze should be wrapped around the tube in an attempt to reduce trauma to the lips and weigh the mask down.¹⁶

'Pregnancy 1' (Table 1) had an emergency caesarean section because of breech presentation. A general anaesthesia was given because spinal and epidural anaesthesia were contraindicated due to infected ulcers in the lumbosacral area.⁴ A face mask saturated in lubricant gel and hydrocortisone ointment allowed general anaesthesia induction. There were no associated skin complications reported as a result of this induction method.⁴ By contrast, a general anaesthetic was deemed to be too dangerous for the patient we recently managed ('pregnancy 9' of Table 1) despite the site of induction of regional anaesthesia being infected with MRSA, which posed a significant risk of bacterial meningitis. These two pregnancies highlight the need for a risk versus benefit approach when it comes to the decision of anaesthesia for caesarean section.

Regional anaesthesia

Regional anaesthesia seems to be more favourable in patients with EB for both emergency and elective caesarean sections

because of the avoidance of airway manipulation.^{15,17} The predominant fear of utilizing this method is the formation of new bullae at the puncture site. However, as shown in the table, five pregnancies underwent regional anaesthesia with no apparent skin complications as a direct result of this anaesthetic method. It is very important that on inspection to determine the puncture site, one meticulously looks for any evidence of infection as this may be a contraindication for regional anaesthesia.⁴ As patients with EB are frequently malnourished, determination of the bony landmarks is often incredibly simple.¹⁶ The skin must be well cleansed with antiseptic spray and any frictional forces of wiping should be avoided.¹⁷ Adhesive tape to secure epidural catheters is contraindicated¹⁷ and instead Mepitac or Mepiform should be used.⁵

During the anaesthesia for labour or delivery

Before the surgery, all staff should be educated on the fragility of the skin and should be reminded of the importance of not leaning on the patient.⁵ It is recommended that the patient should position themselves and be anaesthetized in the operating theatre in order to avoid multiple patient transfers.¹⁸ During the surgery, there are a number of techniques that should be adhered to in order to avoid the development of new blisters or exacerbate pre-existing ones. It is important to remember that friction and shearing forces are mostly responsible for new bullae formation.¹⁸ Therefore, precautions should be taken at all times to reduce friction, especially with regard to the use of theatre equipment. Examples of items that should be avoided include medical adhesive tapes, diathermy pads, Patslide and rigid nasogastric tubes. Monitoring devices, such as electrocardiograms, pulse oximeters and blood pressure cuffs, should be carefully padded to avoid friction.⁵ It has been advised to allow maximal intervals between blood pressure measurements during surgery in these patients.¹⁹

Postnatal care

There are few reported postnatal complications (Table 1). Consequently, patients with EB usually have similar postnatal inpatient stays to non-EB-affected patients. Of note, it has been suggested that compression stockings should not be routinely administered due to the unavoidable shearing force they produce on application.⁵ Patients with EB may need extra support from hospital and community midwives in giving practical advice on caring for the baby, especially if the mother's hands are affected by blisters, scarring or pseudosyndactyly.

Breast feeding

Breast feeding is not contraindicated in women with EB. Five women breast fed in the postnatal period, although there was a high rate of blister formation around the nipples reported (Table 1). The blister formation resulting in difficulty with breast feeding has been reported in the literature,⁷ yet some women have managed to continue for a number of months. The mother should be educated to position the neonate's mouth correctly around the part of the areola that has tougher skin.⁵ Well-lubricated nipple shields should be offered to all mothers in order to reduce bullae formation.

Future implications

Despite the few reported pregnancies in the literature, this review highlights that patients are able to successfully have more than one pregnancy. Clinical genetics consultations should be offered to both male and female patients with EB considering pregnancy in order to educate and convey the risks of inheritance.²⁰ Prenatal diagnosis of EB is now being practised in specialized centres using chorionic villus sampling.²¹ Preimplantation genetic diagnosis of some forms of EB has recently been licensed allowing for more choice of families at risk of recurrence of EB.²¹

As women with EB are able to have successful pregnancies, the importance of documenting all deliveries should be stressed, especially in those women who are known to have a neonate affected by EB. There is a need to gather evidence to allow an understanding of the optimum delivery for these neonates. Of course, long-term paediatric dermatology follow-up should be arranged following birth for all affected children.

CONCLUSION

In conclusion, EB is a severe disabling skin condition which often leads to misconceptions surrounding pregnancy, and the need for increased considerations of the labour plan. Patients should be informed that pregnancy is not contra-indicated, but as with any woman, they should attempt to achieve optimum physical health and good nutritional balance before trying to conceive. Importantly, there do not appear to be added antenatal complications in this group of pregnancies and the skin condition seems unlikely to worsen as a result of the pregnancy. Vaginal delivery appears to be the most favourable if EB does not significantly affect the genital tract of the patient. If caesarean section is indicated, regional anaesthesia should be recommended as it avoids airway manipulation and minimally affects the skin condition at the puncture site. Pregnancy and childbirth in patients with EB can be managed safely and effectively, but it is important that plans for all situations that may arise at labour are discussed and agreed with the multi-disciplinary team well in advance. There is a need to extensively review more pregnancies and a comprehensive survey of a large cohort of EB families would be invaluable to determine if their personal experiences back up the few pregnancies reported in the literature.

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(Accepted 7 May 2010)