Accepted: 5 June 2024

DOI: 10.1111/1471-0528.17893

BJOG An International Journal of Obstetrics and Gynaecology

SYSTEMATIC REVIEW

Vascular Ehlers-Danlos syndrome and pregnancy: A systematic review

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Abstract

Background: Vascular Ehlers-Danlos syndrome (vEDS) is a hereditary connective tissue disorder associated with an elevated risk of vascular, uterine and digestive complications. Managing pregnancy in this context can be a challenge.

Objectives: To systematically review the literature data on the complications in pregnancy associated with vEDS.

Search strategy: We searched the Pubmed Medline and Embase databases for articles using the following terms "vascular Ehlers-Danlos syndrome" or "vEDS" AND "pregnancy".

Selection criteria: Women with vEDS.

Data collection and analysis: We searched the PubMed® MEDLINE® database for publications evaluating obstetric outcomes in women with vEDS.

Main results: A total of 121 publications were screened, with six (accounting for 412 pregnancies) included in our review. Of the women included in this sample, 30% were infertile. The miscarriage rate was 13.8% (57/412) and 8.8% of the live births were premature. Obstetric anal sphincter injuries occurred in 11.3% (23/203) of the deliveries. The maternal mortality rate per pregnancy was 5.7%.

Conclusions: Women with vEDS present an elevated risk of uterine rupture, vascular events, digestive events and death during pregnancy. Women appear to be most at risk during the peripartum period; to avoid expulsive efforts, a caesarean section should be scheduled at 37 weeks of gestation.

KEYWORDS
obstetrics, pregnancy, vascular Ehlers-Danlos syndrome

1 | INTRODUCTION

Ehlers-Danlos syndrome (EDS) corresponds to a heterogeneous group of rare, inherited, connective tissue disorders, characterised by joint hyperlaxity, high skin elasticity and connective tissue fragility.[1] In the general population, the estimated prevalence of EDS is 1/5000.[2] In 2017, the international classification was revised to include 13 subtypes, of which classic EDS, hypermobile EDS and vascular EDS (vEDS) are the most frequent. With the exception of the hypermobile subtype, a number of disease-causing mutations in genes encoding connective tissue proteins have been identified; this genetic diagnosis has made it possible to identify and differentiate between the various subtypes.[1]

Formerly referred to as type-IV EDS, vEDS is an autosomal dominant disease with a prevalence of 1–9/100 000. It is most often associated with a mutation in *COL3A1* or, more rarely, *COL1A1*, which respectively code for type-III and type-I procollagen chains.[1] Type-III collagen is found in the skin, vessel walls and viscera, where it provides structural robustness.[3]

Vascular EDS is one of the most severe disease subgroups because its complications are potentially life-threatening.[3] After having taken the patient's family medical history into account, the major clinical diagnostic criteria for vEDS include the occurrence of spontaneous colon perforation, uterine rupture during pregnancy, in the absence of a previous caesarean section, and/or severe peripartum perineal tears, arterial rupture before the age of 40 years and the formation of a carotid cavernous sinus fistula, in the absence of trauma.[1] These complications are rare in childhood, but affect 25% and 80% of patients before the ages of 20 and 40 years, respectively.[3] Further, vEDS may be accompanied by skin abnormalities (e.g. thin, translucent skin and spontaneous bruising), hyperlaxity in small joints, tendon/muscle rupture and spontaneous pneumothorax.[1] In contrast, hypermobility in large joints and skin hyperextensibility are unusual in vEDS.[3] However, certain *COL3A1* gene variants are associated with a less severe vEDS phenotype. Indeed, patients with haplo-insufficient variants have a milder course of vEDS and may not suffer from digestive tract complications.[4] However, data on complications of pregnancy in women with these *COL3A1* gene variants are lacking. The true prevalence of vEDS is poorly known, and the disease is probably under-diagnosed.[3]

In view of the clinical manifestations of vEDS, pregnancy is a challenge. Women with vEDS are more likely to suffer from complications of pregnancy. Women appear to be particularly at risk during the perinatal period (i.e. the intrapartum and immediate postpartum periods), owing to the onset of contractions in a uterus that has often already been weakened. It has been suggested (but not demonstrated) that uterine contractions also increase the heart rate, blood pressure and intra-abdominal pressure, which in turn accentuates the risk of blood vessel rupture or dissection and hollow-organ perforation.[5] Uterine contractions are not the only cause of high blood pressure, as blood pressure is also elevated during pregnancy in general. Furthermore, the underlying mechanisms are not fully understood. The European Society of Cardiology advises against pregnancy in patients with vEDS.[6] The American College of Obstetricians and Gynecologists (ACOG) also recommends avoiding pregnancy and discussing abortion if a women with vEDS does become pregnant.[7] Lastly, the American College of Cardiology (ACC) and the American Heart Association (AHA) do not recommend against pregnancy in low-risk populations (i.e. women with a null mutation and normal imaging findings).[8] A few studies reporting data on mortality and morbidity rates in pregnant women with vEDS have been published. We therefore decided to systematically review the literature on the complications of pregnancy in women with vEDS.

2 | METHODS

The present report complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards and followed a prespecified protocol. The review was registered in the PROSPERO database (CRD42024504626).

2.1 | Search and selection criteria

We searched the PubMed® MEDLINE® and Embase (Excerpta Medica Database) databases for English- and French-language articles published between January 1980 and June 2023, using the following terms: 'vascular Ehlers-Danlos syndrome' OR 'vEDS' AND 'pregnancy'. The reference lists of literature reviews, meta-analyses and observational cohort studies were used to identify additional publications. Eligible publications were assessed according to pre-established inclusion criteria: (i) observational cohort studies, case–control studies and case reports; (ii) publications written in English or French; (iii) inclusion of patients with vEDS; and (iv) the reported data on pregnancy. Two investigators (TH and AF) independently reviewed the titles and abstracts and selected publications for analysis of the full text. We decided to include case reports in our review because they provided extremely interesting data that were not available in cohort studies. When data were available, we collected information about the patients' pregnancies. However, we did not include case report data in our analysis of the cohort studies, which is described separately. Letters to the editor, literature reviews (including meta-analyses) and expert opinion articles were excluded.

2.2 | Data collection

The following data were collected independently by two investigators (TH and AF) and reported according to a standardised scheme: the characteristics of the publication (the names of the authors and the date of publication), the study country, the population source, the number of patients, pregnancies, deliveries and live births, infertility, complications during the first trimester (early spontaneous miscarriage and ectopic pregnancy), complications during pregnancy in general (threatening preterm labour), preterm premature rupture of membranes (PPROM), delivery, postpartum death and maternal death.

2.3 | Definitions

The peripartum period was defined as the period around childbirth. The postpartum period was defined as the period after childbirth (6 weeks after delivery).

3 | RESULTS

3.1 | Database search

The above-described search strategy identified a total of 121 publications. After the removal of duplicates and analysis of the abstracts, 43 publications were found to be eligible. Of these, eight were excluded because they were systematic reviews that did not specifically mention vEDS. The full texts of 35 publications were analysed. Three publications on cohort

studies reported on complications of pregnancy in women with EDS but did not differentiate between EDS subtypes. One publication about a cohort study did not collect data on pregnancy (Figure 1). Ultimately, six observational cohorts and 25 cases described in case reports were included in our analysis (Table S1). The six included cohort studies encompassed a total of 412 pregnancies in women with vEDS. None of the cohort studies specified whether each woman's vEDS had been diagnosed before pregnancy or not.

3.2 | Fertility

The study by Hurst et al. was the only one to provide data on fertility.[9] The proportion of infertile patients was significantly lower in the vEDS subgroup (9/30) than in the hypermobile subgroup (170/357) (30% vs 47.6%, respectively; $P = 0.026$). The difference between the vEDS subgroup and the classic subgroup was not statistically significant. There were several causes of infertility. The proportion of women with infertility related to a uterine anomaly was higher in the vEDS subgroup (2/9) than in the hypermobile (5/172) and classic (3/31) subgroups (22.2%, 2.9% and 9.7%, respectively; $P = 0.014$). However, the exact type of uterine anomaly was not specified. There were also cases of voluntary childlessness, as 62.5% (20/32) of the patients with vEDS had been advised against becoming pregnant. This proportion was significantly higher for the hypermobile subgroup 21% (171/557) and for the classic subgroup 22.5% (29/129) than for the other EDS subtypes ($P < 0.001$).

3.3 | Complications in the first trimester

Six cohort studies (encompassing 412 pregnancies) had evaluated first-trimester complications.[3,5,9–12] The overall

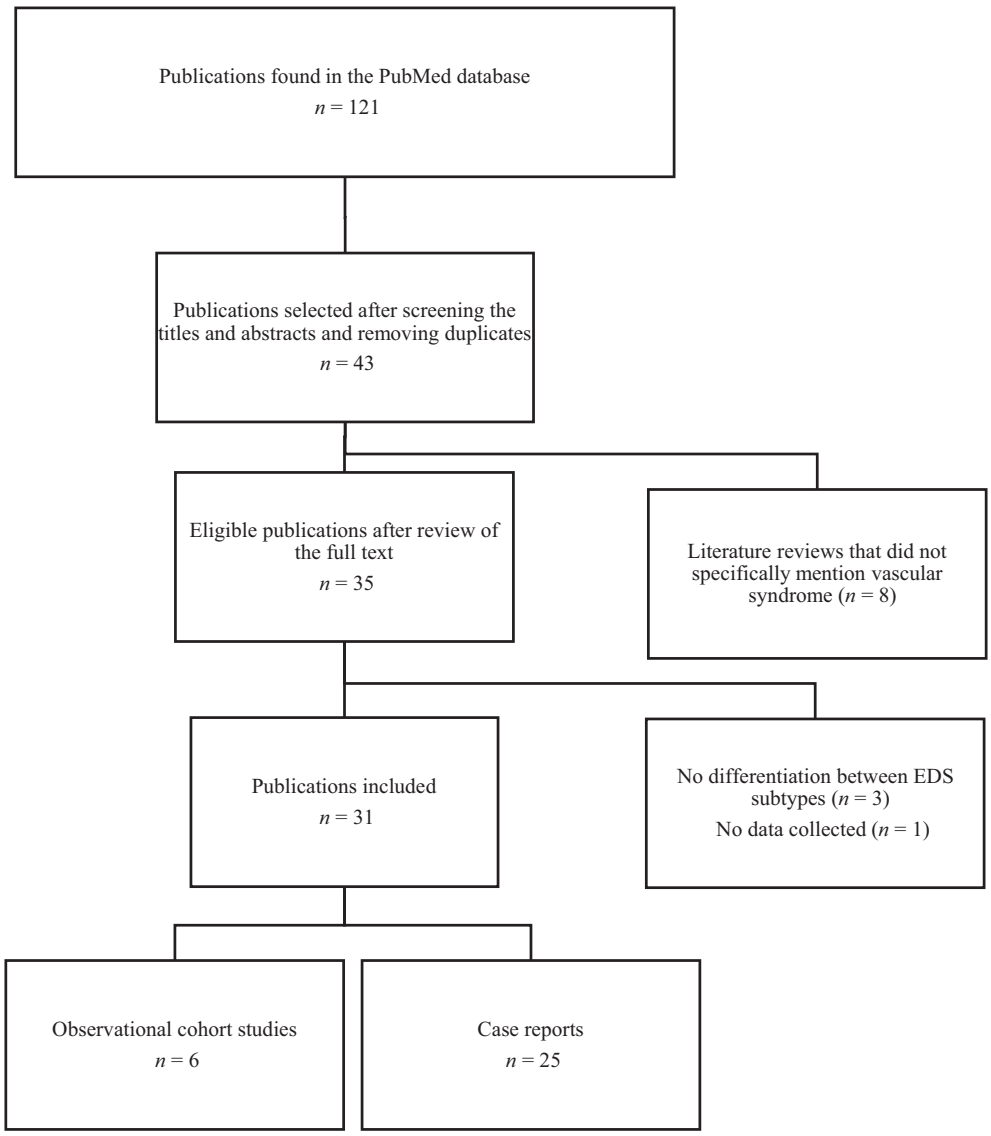

FIGURE 1 Flow chart for the inclusion of studies in the systematic review.

early spontaneous miscarriage rate ranged from 5.5% to 46.2% (with an overall mean value of 13.8%, 57/412; Table 1). Unfortunately, none of the studies put forward a hypothesis to explain these miscarriage rates. Only one study compared early spontaneous miscarriage rates in the three main subtypes of EDS; no significant differences were found.[9] In these six studies, the overall ectopic pregnancy rate was 0.9% (4/412). Hurst et al. did not find significant differences in the ectopic pregnancy rate between the three main subtypes of EDS.[9]

3.4 | Mode of delivery and term of birth

Of the 412 pregnancies recorded, 310 (75.2%) resulted in full-term delivery and 30 (7.3%) resulted in premature delivery (Table 2). Relative to the number of live births, the premature delivery rate was 8.8% (30/340). There were more vaginal deliveries (65/99) than caesarean deliveries (34/99) (65.7% vs 34.4%, respectively). However, the mode of delivery was known for only 99 of the 334 births (29.6%). For the 99 pregnancies in the study by Hurst et al., it was not specified whether the vEDS had been diagnosed before pregnancy. Of the 34 caesarean sections, 28 (82.4%) were scheduled.

3.5 | Non-life-threatening obstetric complications

Few of the cohort studies reported details of non-life-threatening obstetric complications (Table 2). The proportion of women with an obstetric anal sphincter injury (OASI) was 11.3% (23/203) when considering all the patients in the four studies with data on OASIs.

Threatening premature labour and PPROM were evaluated in one study.[10] Murray et al. recorded two cases of placental abruption.[5] The lack of data prevented any comparisons (Table 2).

3.6 | Major complications

We next considered major life-threatening complications (defined as vascular dissection and uterine/intestinal rupture without death) and maternal deaths (Table 3). Major complications (other than maternal death) were more likely to occur postpartum (3%, representing 5/166 patients from the three studies with data on major complications other than death) than during pregnancy (1.8%, $n=3$) or during delivery (0.6%, $n=1$).

Dubruc et al. described two major complications: one patient had a ruptured mitral valve abutment on day 6 after a vaginal delivery, and the other suffered from a ruptured caecum on day 6 after a caesarean section under general anaesthesia.[10]

3.7 | Maternal deaths

The overall maternal death rate was 5.7% (22/386 patients from the five studies with data on maternal death) (Table 4). Death was more frequent during delivery (3.1%, 12/386) than during the other two periods (Table 4A). More than half of the deaths occurred during the peripartum period (54.5%, 12/22), with two deaths occurring during a vaginal delivery and one death occurring during a caesarean section. For the remaining nine deaths, the mode of delivery was not known. More maternal deaths resulted from vascular rupture or dissection (63.6%, 14/22) than from uterine rupture (31.8%, 7/22) or the rupture of other organs (4.6%, 1/22) (Table 4). Murray et al. reported five cases of maternal death: two deaths were related to aortic dissection during labour, another was related to aortic dissection 7 days after a scheduled caesarean section for breech presentation, the fourth was associated with rupture of the iliac artery after a fall at 33 weeks of gestation and the fifth death was attributed to hysterotomy closure dehiscence after a scheduled caesarean section at 36 weeks of gestation.[5] In the same study, the non-lethal complications attributable to vEDS were a coronary artery dissection during pregnancy, a splenic artery dissection on day 6 after a vaginal delivery, multiple arterial dissection on day 7 after a vaginal delivery, two uterine ruptures (one before labour and one during labour), and a bladder and vein tear during a scheduled caesarean section for breech presentation.[5]

In a study of ten patients with 26 pregnancies, Rudd et al. described one major complication: a colon rupture after 8 weeks of gestation. There were five deaths: two women died of uterine rupture during labour, one died of uterine rupture and vascular dissection during labour, and two died from vascular rupture in the immediate postpartum period.[12]

In a study of 81 women (183 pregnancies) reported by Pepin et al., 12 died: five died of uterine rupture during labour, two died of vascular dissection during labour and five died of vascular dissection postpartum. The cumulative number of pregnancies did not appear to markedly influence the death rate, which was 6.2% (5/81) among women with one pregnancy, 5.6% (3/53) among women with two pregnancies, 8.3% (2/24) among women with three pregnancies and 15.3% (2/13) among women with five pregnancies (13 patients).[3]

3.8 | Analysis of case reports

When considering the 25 case reports found in the literature, all maternal deaths ($n=9$) were related to vascular rupture/dissection.[13–36] At the time of death, none of the nine women had been diagnosed with vEDS. Four of the seven women with data (57.1%) had a family history of illness in early pregnancy, which should perhaps have prompted further diagnostic assessment.

When the vEDS had been diagnosed before delivery, ten women had a scheduled caesarean section and five women

TABLE 1 Complications in the first trimester and mode of delivery.

	Pregnancies	ESM	EP	VD	CS
Authors	***n***	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Dubruc et al.	27	3 (11.1)	0	18 (78.3)[b]	5 (21.7)[b]
Hurst et al.	26	12 (46.1)	2 (7.7)	47 (61.8)[b]	29 (31.2)[b]
Rudd et al.	26	0	0	NR	NR
Murray et al.	113	26 (23)	1 (0.9)	NR	NR
Pepin et al.	183	10 (5.5)	0	NR	NR
Gilchrist et al.	37	6 (16.2)	1 (2.7)	NR	NR
Total	412	57 (13.8)	4 (0.9)	65 (65.7)[a]	34 (34.3)[a]

Abbreviations: CS, caesarean section; EP, ectopic pregnancy; ESM, early spontaneous miscarriage; NR, not reported; VD, vaginal delivery.

[a]Based on the number of pregnancies for which data were available.

[b]Based on the number of deliveries.

had a vaginal delivery. Only one woman with vEDS known prior to pregnancy died (6 days after her vaginal delivery, from a ruptured right renal artery).

None of the women who had a scheduled caesarean section died. For one of the patients, however, a myometrial tear made closure of the hysterotomy difficult. This difficulty was not described for the other women having had a caesarean section. Of the 16 women not diagnosed with vEDS prior to pregnancy, 12 of the 14 with data (85.7%) had a family history suggestive of the disease. It is therefore essential to ask patients about their family history at the start of pregnancy, so as not to miss a possible diagnosis of vEDS.

In a study of maternal deaths recorded in France between 2001 and 2012, 0.2% (2/973) were attributable to a major complication in the context of vEDS.[37] Two women died before labour: one died of the rupture of the right external iliac artery at 39 weeks of gestation and the other died of the rupture of the gastroepiploic artery at 38 weeks of gestation.[37]

4 | DISCUSSION

4.1 | Main findings and interpretation

Our objective was to review and summarise obstetric data (from first-trimester complications to postpartum complications) for women with vEDS. Only one study looked at the infertility rate among women with vEDS: a value of 30% (9/30) was found.[9] Worldwide, between 8% and 12% of couples are infertile.[38] However, it is difficult to assess voluntary childlessness arising from a fear of: (i) complications of vEDS during pregnancy; and (ii) the transmission of vEDS to the child. In the study by Hurst et al., almost two-thirds of the patients were advised against becoming pregnant.[9]

Early spontaneous miscarriage is the most common complication of pregnancy. In our review, the overall early spontaneous miscarriage rate was 13.8% (57/412). This value is close to the early spontaneous miscarriage rate of 12% found in a 2008 study of 1200 pregnancies in the general population.[39] However, this result must be interpreted with caution, given the great inter-study differences in early spontaneous miscarriage rates. Furthermore, none of the studies made any hypotheses about the causes of these early spontaneous miscarriages or evaluated these rates in relation to known risk factors (e.g. age, a high body mass index, active smoking, a history of early spontaneous miscarriage, and low ovarian reserve). Maternal death following early spontaneous miscarriage is extremely infrequent, with an estimated incidence of 0.05–0.22/100 000 pregnancies.[40] Our review did not identify any cases of maternal death from early spontaneous miscarriage. There is no evidence to suggest that vEDS influences the likelihood of an aneuploid embryo. This might explain why the miscarriage rate in patients with vEDS is similar to that observed in the general population.

In our review, the ectopic pregnancy rate was significantly lower among women with vEDS than in the general population. In a study of over 120 000 pregnancies in the general population, the estimated rate of ectopic pregnancy was 2%.[41] The estimated mortality rate from ectopic pregnancy in the general population is 0.36 per 100 000 live births.[42] Our review did not identify any cases of maternal death following ectopic pregnancy.

The results of some studies have suggested that the risk of premature delivery is abnormally high in patients with vEDS, as a result of cervical insufficiency and/or the premature rupture of membranes.[5] In France, the prematurity rate in 2021 was 7%.[43] In our review, 8.8% (30/340) of the live births occurred before 37 weeks of gestation: this proportion is similar to that seen in the general population. The cohort studies reviewed here provided few details on the causes of premature delivery. Only one study reported that the proportion of women with threatening preterm labour was 8.7%.[10] vEDS *per se* does not appear to be a risk factor for premature delivery.

In our review, the caesarean section rate was 34.3% (34/99 deliveries with data). This high value might be associated with the elevated proportion of scheduled caesarean sections (82.4%, 28/34). As mentioned above, the mode of delivery was specified for only 99 of the 334 pregnancies (29.6%). Moreover, vEDS had not been diagnosed prior to pregnancy in all cases. If a woman is known to have vEDS, a caesarean

TABLE 2 Obstetric complications.

Authors	Pregnancies *n*	Term birth *n* (%)	Premature delivery (<37 weeks of gestation) *n* (%)	PPROM *n* (%)	TPL *n* (%)	Placental abruption *n* (%)	Stillbirth *n* (%)	OASI *n* (%)	Haemorrhage *n* (%)
Dubruc et al.	27	23 (85.2)	0	1 (3.7)	2 (7.4)	NR	0	5 (18.5)	2 (7.4)
Murray et al.	113	65 (57.5)	17 (15)	NR	NR	2 (1.7)	0	16 (14.2)	8 (7)
Hurst et al.	26	15 (57.7)	11 (42.3)	NR	NR	NR	0	NR	NR
Rudd et al.	26	17 (65.4)	1 (3.8)	NR	NR	NR	0	1 (3.8)	2 (7.7)
Pepin et al.	183	167 (91.2)	0	NR	NR	NR	3 (1.6)	NR	NR
Gilchrist et al.	37	29 (78.4)	1 (2.7)	NR	NR	NR	0	1 (2.7)	NR
Total	412	310 (75.2)	30 (7.3)	1 (3.7)[a]	2 (7.4)[a]	2 (1.7)[a]	3 (0.7)	23 (11.3)[a]	12 (7.2)[a]

[a]Based on the number of pregnancies for which data were available.

Abbreviations: NR, not reported; OASI, obstetric anal sphincter injury; PPROM, preterm premature rupture of membranes; TPL, threatening premature labour.

section can be recommended.[6,8] These considerations might explain the high observed caesarean section rate. In this at-risk population, an emergency caesarean section may be performed in the event of serious life-threatening complications (whether obstetric or not) during pregnancy or labour.

In the general population, the estimated OASI rate is between 0.25% and 6.0%[44]; in our review, we found a value of 11.3% (23/203). This higher rate can be explained by the fragility of tissue observed in women with vEDS. Many cohort studies and case reports have described the difficulty of suturing perineal tears and hysterotomy closure during caesarean sections. It should be noted that between 35% and 60% of women with an OASI at the time of delivery will develop long-term faecal incontinence.[44] However, learned societies in Europe and the USA recommend a scheduled caesarean section for patients with vEDS. If vaginal delivery is authorised on a case-by-case basis, extreme caution should therefore be exercised. There are no guidelines on the use of non-absorbable sutures after caesarean sections.

In our review, the incidence of major complications (vascular dissections and organ ruptures, excluding death) linked to vEDS was 5.4%. Some of these complications occurred during pregnancy or delivery. The period of highest risk was the postpartum period, with a major complication rate of 3%. Given the small number of women studied, no risk factors for major complications could be identified. During the postpartum period, there were more major complications after vaginal birth than after caesarean section. Again, given the small numbers involved, these findings should be treated with caution.

We noted 22 deaths in the cohort studies, more than half of which occurred during the delivery period. All the deaths were related to vascular rupture or uterine rupture. This high mortality rate during labour might encourage clinicians to systematically schedule a caesarean section before labour for pregnant women with vEDS. We note that none of the patients who underwent a scheduled caesarean section died. Difficulties with closure and the presence of a myometrial tear were only described in one study. Scheduled caesarean section therefore appears to reduce the risk of maternal death. However, there are few data on complications and surgical difficulties during caesarean sections.

In view of all these factors, a scheduled caesarean section appears to be appropriate for pregnant women with vEDS. Indeed, expulsive efforts might lead to major complications, such as uterine rupture or vascular dissection. Similarly, the high OASI rate found in our review suggests that vaginal delivery is not advisable. However, the scarcity of data prevents us from drawing any firm conclusions. We found that vaginal delivery accounted for over 65% of the deliveries with data. Furthermore, the currently available data do not enable us to say whether major complications occurred more frequently after a vaginal delivery or after a caesarean section.

The European Society of Cardiology advises against pregnancy in women with vEDS because of the high risk of arterial rupture.[6] The American College of Cardiology (AAC)/American Heart Association (AHA) do not advise against

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TABLE 3 Major complications that did not lead to maternal death.

		Major complications without maternal death					
			During delivery		Postpartum		
Authors	Pregnancies *n*	During pregnancy *n* (%)	VD *n* (%)	CS *n* (%)	After VD *n* (%)	After CS *n* (%)	Total *n* (%)
Dubruc et al.	27	0	0	0	1 (3.7)	1 (3.7)	2 (7.4)
Murray et al.	113	2 (1.9)	0	1 (0.9)	3 (2.7)	0	6 (5.3)
Rudd et al.	26	1 (3.8)	0	0	0	0	1 (3.8)
Pepin et al.	183	NR	NR	NR	NR	NR	NR
Gilchrist et al.	37	NR	NR	NR	NR	NR	NR
Total	386	3 (1.8)[a]	0	1 (0.6)[a]	4 (2.4)[a]	1 (0.6)[a]	9 (5.4)[a]

Abbreviations: CS, caesarean section; NR, not reported; VD, vaginal delivery.

[a]Based on the number of pregnancies for which data were available.

TABLE 4 Maternal death and causes of death.

		Maternal deaths							
				During delivery			Postpartum		
Authors	Pregnancies *n*	During pregnancy *n* (%)	Delivery mode NR *n* (%)	VD *n* (%)	CS *n* (%)	Delivery mode NR *n* (%)	After VD *n* (%)	After CS *n* (%)	Total *n* (%)
Dubruc et al.	27	0	0	0	0	–	0	0	0
Murray et al.	113	1 (0.9)	–	2 (1.8)	0	–	0	2 (1.8)	5 (4.4)
Rudd et al.	26	0	2 (7.7)	–	1 (3.8)	2 (7.7)	–	–	5 (19.2)
Pepin et al.	183	0	7 (3.8)	–	–	5 (2.7)	–	–	12 (6.6)
Gilchrist et al.	37	0	0	0	0	0	–	–	0
Hurst et al.	26	NR	NR	NR	NR	NR	NR	NR	NR
Total	386	1 (0.26)	9 (2.3)	2 (0.5)	1 (0.3)	7 (1.8)	0	2 (0.5)	22 (5.7)

		Cause of death			
	Maternal death	Vascular rupture/dissection	Uterine rupture	Hollow-organ perforation	Unknown
Authors	*n*	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Murray et al.	5	4 (80)	0	1 (20)	0
Rudd et al.	5	3 (60)	2 (40)	0	0
Pepin et al.	12	7 (58.3)	5 (41.7)	0	0
Total	22	14 (63.6)	7 (31.8)	1 (4.6)	0

Abbreviations: CS, caesarean section; NR, not reported; VD, vaginal delivery.

pregnancy in a low-risk population (women with specific genetic variants, null mutations and normal vascular imaging). Vaginal delivery could be considered if the aortic diameter is below 4.0 cm and there is no history of chronic aortic dissection. In all other cases, a caesarean section is recommended.[8] In the event of pregnancy, the patient should receive rigorous, multidisciplinary follow-up. The aorta must be monitored echocardiographically on a regular basis during pregnancy and 6 months after delivery; the exact frequency (e.g. from once a month to once every 3 months) will depend on the risk of aortic dissection. However, women can have aneurysms and dissection in vessels that cannot be monitored using ultrasound. Contrast-free magnetic resonance angiography is a possible option.[45,46] Pregnant women with vEDS should be offered preventive treatment with beta blockers, to reduce the risk of vascular complications.

Although we are aware of the major biases involved, we decided to analyse case reports because they provided extremely interesting data that are not available in cohort studies. Induced prematurity might be one explanation for the level of prematurity in this population. In fact, some women with a diagnosis of vEDS at the time of pregnancy had a scheduled caesarean section before 37 weeks of gestation. We note that the great majority (85.7%) of patients not

diagnosed with vEDS at the time of pregnancy had a suggestive family history. We believe that it is important to carry out an in-depth investigation of the patient's personal and family medical history at the start of pregnancy. Our review of cohort studies showed that the death rate during labour was high. This finding might encourage certain clinicians to systematically prescribe a caesarean section before labour for pregnant women with vEDS. This approach was mentioned in case reports: the fear of severe or fatal complications prompted clinicians to schedule a caesarean section, sometimes even before 37 weeks of gestation. We note that none of the women who underwent a scheduled caesarean section died.

4.2 | Strengths and limitations

This study is the first systematic review of obstetrical and maternal complications in patients with vEDS. However, the review had several limitations. The proportion of missing data was high in some source publications. Some of the complications that occurred during these patients' pregnancies were probably not reported. We also found few details of the mode of delivery, such as the overall duration of labour and the duration of expulsive efforts for vaginal delivery. The results should therefore be interpreted with caution. As with all systematic reviews of observational and retrospective data, the interpretation of the results is limited by the number, quality and homogeneity of the included studies. Although a few studies controlled for important variables, adjusted odds ratios or standardised mean differences were rarely reported.

In future studies, it would be interesting to collect data on the pre-pregnancy history of vEDS complications, whether the diagnosis of vEDS was made before pregnancy or not, and precisely defined complications occurring during pregnancy. In the case of vaginal delivery, it would be useful to know the reason for authorising this method of delivery, the duration of labour, the duration of expulsive efforts, the use of instrumental extraction, the occurrence of tears, the quality of the suturing and the quality of healing. In the event of a scheduled caesarean section, it would be preferable to record the justification (indication), the term or pregnancy, and the quality of the uterine suturing.

5 | CONCLUSION

Women with vEDS have elevated risks of uterine rupture, vascular rupture, digestive perforation and death during pregnancy. The patient's cardiologist should initiate treatment with beta blockers and monitor aortic dilatation. The risk of death appears to be greatest during delivery; hence, to avoid expulsive efforts, a scheduled caesarean section should be considered before labour (e.g. at 37 weeks of gestation). However, the postpartum period should not be overlooked because serious complications can also arise then.

AUTHOR CONTRIBUTIONS

TH: data collection and writing and revising the article. BB: drafting and revising the article. AD: drafting and revising the article. JG: revising the article. JS: revising the article. AF: data collection and drafting and revising the article.

ACKNOWLEDGEMENTS

None.

FUNDING INFORMATION

This research did not receive any specific funding from agencies or organisations in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest in relation to this work.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author, upon reasonable request.

ETHICS APPROVAL

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Haem T, Benson B, Dernoncourt A, Gondry J, Schmidt J, Foulon A. Vascular Ehlers-Danlos syndrome and pregnancy: A systematic review. BJOG. 2024;00:1–10. https://doi.org/10.1111/1471-0528.17893