High-risk pregnancies in Diamond-Blackfan anemia: a survey of 64 pregnancies from the French and German registries

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We reviewed 64 pregnancies in 26 women with Diamond-Blackfan anemia (DBA) included in the French and German DBA registries. Complications were seen in 42 pregnancies (66%) and included abortion, pre-eclampsia, *in utero* fetal death, intrauterine growth retardation, retroplacental hematoma, pre-term delivery and fetal malformations. Of the 34 children (53%) born alive, 13 had DBA. No correlations were found between pregnancy outcome and features of either maternal or child DBA. Pregnancies in DBA-affected women are at high risk, especially for complications likely to be of vascular-placental origin. Careful monitoring with prevention of severe anemia and early introduction of aspirin is suggested.

Key words: Diamond-Blackfan anemia, pregnancies, vascular placental complications.

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Diamond-Blackfan anemia (DBA) is a rare, congenital, pure red blood cell aplasia which presents in early infancy. Forty percent of patients have congenital abnormalities.[1,2] Even though DBA is commonly sporadic, in 10-20% of cases a family history of DBA follows an autosomal dominant pattern.[2] Mutations within the gene encoding ribosomal protein S19 (*RPS19*) are found in 25% of patients.[3] Increased erythrocyte adenosine deaminase (eADA) activity is often noted, and *RPS19* gene mutations may also be found in some apparently unaffected family members.[3-4] Although anemia may initially respond to steroid therapy, up to 40% of patients will finally require life-long regular red blood cell transfusions.[2] The few data available concerning pregnancies in DBA-affected women suggest a high incidence of complicated pregnancies.[5] Here we report on a survey of 64 pregnancies in women registered in the French and German DBA registries.

Design and Methods

Sixty women (18-58 years) were recruited from the French (41 women) and German (19 women) DBA registries initiated respectively 20 and 7 years ago.[2] The German registry includes affected children and, through this bias, affected mothers. Thirty-four women had not had a pregnancy for various reasons, including 14 for medical reasons (infertility (n=4) and co-morbidities (n=10)), and are not considered further in this study. Among the 26 women who had had at least one pregnancy, 19 were checked for *RPS19* gene mutations: nine have a mutation and ten have the wild-type sequence. Tables 1 and 2 indicate treatment prescribed at the time of any pregnancy. Detailed clinical information on pregnancies (number, outcome, therapeutic changes) and fertility were obtained from the patient herself or from the referring physician. Because of missing data, no study on iron status was possible. Results were analyzed in terms of therapeutic and genetic status and whether or not the child was affected by anemia and malformations. An uncomplicated pregnancy was defined as follows: absence of maternal hypertension during the course of the pregnancy, delivery after 36 weeks of gestation, birthweight above the tenth centile and absence of fetal malformations. All children were followed-up, with particular attention in cases of anemia or malformations.

Results and Discussion

The mean age of the women at the time of this study and at their first pregnancy was 35.3 and 24 years, respectively. The mean number of pregnancies was 2.4. Of 64 recorded pregnancies, 42 were complicated (66%, Table 1) and 22 uncomplicated (Table 2). Both complicated and uncomplicated pregnancies could be observed subsequently in the same individual. In eight women, all pregnancies were uneventful. Complications included fetal losses (26/42, including two abortions for medical or personal reasons), pre-eclampsia (5/42, resulting in 2 *in utero* fetal deaths and in three pre-term deliveries), isolated pre-term delivery (4/42, one being a twin pregnancy and two in a context of gestational diabetes), *in utero* fetal death (3/42, two being associated with retro-

Table 1. Patients with DBA and at least one complicated pregnancy.

Mother				Pregnancy					Offspring	
Patient number	*Age (years)*	*RPS19 gene mutation*	*Previous therapy*	*Number*	*Age*	*Therapy*	*Outcome*	*Alive/ death*	*DBA status*	*RPS19 gene mutation*
1	27	280C→T	T, C	1	26	↑T	Pre-eclampsia, born preterm at 29 WG, IUGR (870g)	A	Unaffected	–
2	37	390delTC	None	1	34	None	Fetal loss at 9 WG	D	Fetal loss	NA
				2	35	None	Pre-eclampsia, IUFD at 23 WG, IUGR (390 g), RPH and malformations	D	IUFD	–
3	31	–	S	1	21	S	Fetal loss at 10 WG	D	Fetal loss	ND
				2	22	↑S	Molar pregnancy at 10 WG	D	Fetal loss	ND
				3	29	↑S	Pre-eclampsia, born preterm at 32 WG, IUGR (1070g) and malformations	A	Unaffected	ND
4	32	–	None	1	27	None	IUFD at 20 WG, RPH	D	IUFD	ND
				2	28	T	IUFD at 24 WG, IUGR and malformations	D	IUFD	ND
				3	30	S/T	Twin pregnancy born preterm at 31 WG	A	Unaffected	ND
5	35	-	None	1	20	None	Pre-eclampsia with IUFD at 30 WG, IUGR (800 g)	D	IUFD	ND
6	34	184C→T	None	1	20	None	IUGR (2650g) at term, malformations	A	Unaffected	NA
				2	21	None	Fetal loss at 8 WG	D	Fetal loss	NA
				3	22	None	Fetal loss at 8 WG	D	Fetal loss	NA
				4	25	None	Normal pregnancy, birth at 41.5 WG, 3900g	A	Unaffected	NA
				5	31	None	Fetal loss at 8 WG	D	Fetal loss	NA
				6	32	None	Normal pregnancy, birth at 37.5 WG, 3700g	A	Unaffected	NA
7	33	–	T, C	1	27	↑T	Fetal loss at 19 WG with hydrops fetalis	D	Fetal loss	ND
				2	32	M/T	Fetal loss at 13 WG	D	Fetal loss	ND
8	35	–	T	1	31	T	IUGR (2490 g) at term	A	Unaffected	ND
9	40	NA	None	1	32	S	Preterm at 32 WG	A	Affected	NA
10	46	–	T/S	1	21	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				2	22	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				3	23	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				4	24	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				5	24	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				6	25	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				7	25	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				8	26	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				9	27	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				10	27	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				11	28	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				12	28	T/S	Fetal loss at 8 WG	D	Fetal loss	ND
				13	29	T/S	Normal pregnancy, birth at 40 WG, BW 3500 g	A	Unaffected	ND
11	33	NA	None	1	26	T	Normal pregnancy, birth at 37 SA	A	Unaffected	NA
				2	29	None	Fetal loss at 9 WG	D	Fetal loss	NA
				3	29	None	Fetal loss at 11 WG	D	Fetal loss	NA
				4	30	T	Termination of pregnancy at 13 WG for fetal malformations	D	TOP	NA
12	35	–	T	1	20	T	Fetal loss at 10 WG	D	Fetal loss	ND
13	34	341delA	None	1	24	S	IUFD at 25 WG, IUGR (450 g), RPH	D	IUFD	NA
				2	26	S	Preterm at 34 WG	A	Affected	NA
14	35	–	None	1	33	T	Pre-eclampsia and preterm at 34 WG	A	Affected	ND
15	58	NA	None	1	19	S	Normal pregnancy, birth at 42 WG, BW 4900g	A	Unaffected	NA
				2	20	S	Fetal loss at 10 WG	D	Fetal loss	NA
				3	22	S	Normal pregnancy, birth at 40 WG, BW 3750g	A	Affected	NA
16	24	184C→T	None	1	19	None	Preterm at 34 WG	A	Unaffected	NA
				2	22	None	Normal pregnancy, birth at 38 WG, BW 4130g	A	Affected	184C→T
17	35	NA	Cy	1	30	T/S	Voluntary interruption of pregnancy at 6 WG for increasing anemia	D	Fetal loss	NA
18	35	31del14	None	1	22	None	Preterm at 36 WG with IUGR (1650g) and malformations	A	Affected	ND
				2	25	None	IUGR (2250g) at 41 WG and malformations	A	Affected	ND

A: alive; BW: birth weight; C: chelation therapy; Cy: cyclosporine; D: Death; IUFD: in utero fetal death; IUGR: intrauterine growth retardation; M: metoclopramide; N: normal; NA: not available (DNA not available); ND: not done (not performed in case of absence of RPS19 gene mutation in the mother); RPH: retro-placental hematoma; S: steroids; T: transfusions; TOP: termination of pregnancy; U: unknown; WG: weeks of gestation.

placental hematoma, and 1 with intrauterine growth retardation). Among the 24 spontaneous abortions, one was a mole pregnancy and one was associated with hydrops fetalis leading to fetal death at 13 weeks of gestation.

These 64 pregnancies resulted in only 34 liveborns (56% of all pregnancies). With a follow-up of 1-39 years after birth (mean time for follow-up 10.7 years), 13 offspring had been diagnosed as DBA-affected (41%). In one child, a mutation in RPS19 identical to that of the affected mother was observed, in spite of a normal hematologic status except for an elevated eADA level at 8 years of age (patient 21/pregnancy 2). The proportion of affected offspring was similar whether pregnancies had been complicated or uncomplicated (6/12 live births versus 8/22).

Table 2. Patients with DBA and uncomplicated pregnancies only.

	Mother Age (years)	Mother RPS19 gene mutation	Mother Previous therapy	Pregnancy Number	Pregnancy Age	Pregnancy Therapy	Pregnancy Term (WG)	Offspring BW (g)	Offspring DBA status	Offspring RPS19 gene mutation
19	42	–	S	1	24	U	Full term	N	Unaffected	ND
				2	28	U	Full term	N	Unaffected	ND
20	34	NA	S/T	1	26	U	38	3030	Unaffected	NA
21	32	Del295	None	1	20	None	39	2860	Affected	Del295
				2	24	None	38	2990	Unaffected*	Del295
				3	27	None	39	2970	Unaffected	–
				4	30	None	40	3000	Unaffected	–
22	34	NA	S	1	23	U	Full term	N	Unaffected	NA
23	33	166C→T	None	1	23	None	36	3330	Affected	ND
24	35	34insAG	None	1	20	None	38	2500	Affected	34insAG
				2	29	T	39	2990	Affected	34insAG
25	24	NA	None	1	20	T	36	3270	Unaffected	NA
26	42	–	None	1	18	None	38	3000	Affected	ND
				2	36	None	37	3130	Affected	ND
				3	38	None	38	3000	Unaffected	ND

*BW: Birth weight; N: Normal; NA: Not available (DNA not available); ND: Not done (not performed in case of absence of RPS19 gene mutation in the mother); S: steroids; T: transfusions, U: unknown; WG: weeks of gestation. *Elevated eADA was noted.*

Table 3. Malformations* in the offspring of affected mothers.

	Malformations in the conceptus	Hematologic status of the child	Malformations in the mother	Mutations in the RPS19 gene Mother	Mutations in the RPS19 gene Child
Patient 2, pregnancy 2	Arachnodactyly, 2-3 syndactyly, meconial ileus and auditory canal stenosis	Unknown (early death)	–	+	–
Patient 3, pregnancy 3	Bilateral thumb hypoplasia	Normal (2 years +)	Low-implanted thumbs, aortic insufficiency	–	ND
Patient 4, pregnancy 2	Ventricular septal defect	Unknown (fetal death)	–	–	ND
Patient 6, pregnancy 1	Facial dysmorphism (up-slanted palpebral fissures), Pierre Robin syndrome, micropenis with cryptorchidism, short feet, ouraque cyst and mental retardation	Normal (14 years +)	–	–	ND
Patient 11, pregnancy 4	Anencephaly, cardiac malformation and presence of liver hemosiderosis	Unknown (fetal death)	–	NA	NA
Patient 15, pregnancy 3	Double renal pelvis	DBA	–	–	ND
Patient 18, pregnancy 1	Pierre Robin syndrome, ASD	DBA	–	NA	NA
Patient 18, pregnancy 2	Pierre Robin syndrome, ASD, kidney malformation	DBA	–	NA	NA

*ASD: Atrial septal defect; NA: Not available (DNA not available); ND: Not done (not performed in case of absence of RPS19 gene mutation in the mother). *Facial dysmorphism was not considered as a malformation.*

Three out of 19 live births were affected according to data from the French registry (16%), whereas 11/15 live births were affected according to data from the German registry (73%). This discrepancy is related to the above mentioned recruitment bias.

Malformations were noted in eight children (Table 3) and, importantly, not exclusively found in DBA-affected offspring. For example, malformations were observed in a genetically normal (as far as *RPS19* was concerned) infant who died shortly after birth and whose mother had a *RPS19* mutation (patient 2/pregnancy 2). Another mother without the *RPS19* mutation delivered a child with malformations who had no anemia after 14 years of follow-up (patient 1/pregnancy 6). In most cases of children with malformations (7/8), the mother has no malformation. A pathological examination of the placenta was available in four cases (patient 1/pregnancy 1, patient 3/pregnancy 3, patient 4/pregnancy 2, patient 12/pregnancy 1) and revealed significant infarctions in three. Investigations of the causes of fetal death or recurrent spontaneous abortion in patients 4, 5 and 14 remained negative. Daily low-dose aspirin and low-molecular-weight heparin were prescribed at 6 and 10 weeks of gestation, respectively, for the third pregnancy of patient 4, who had previously

experienced two fetal deaths: the outcome was favorable, except for a preterm delivery potentially related to the twin pregnancy.

RPS19 mutations were present in women with complicated and uncomplicated pregnancies. The small size of the two subpopulations prevents a statistical study (Tables 1 and 2). Among the 26 women with at least one pregnancy, ten were receiving treatment while 16 were off treatment (Tables 1 and 2). Among the 18 women with complicated pregnancies, 10 were off treatment; among the 8 women in whom all pregnancies were uncomplicated, five were off treatment. Decreases in transfusion-free intervals or increases in steroid dosage during pregnancy were often observed (Tables 1 and 2). Out of 15 patients who were previously treatment independent, five required transfusions and three steroid therapy for satisfactory control of anemia during pregnancy. Finally, 11 out of 26 women required institution of treatment or an increase of treatment during pregnancy. Hemoglobin levels were maintained above 9-10 g/dL during most of the pregnancies, but were occasionally difficult to monitor (patients 4 and 7).

We surveyed 64 pregnancies in 26 patients out of a population of 60 DBA-affected women. We found a high occurrence of complications in both mothers and children. Complications related to a situation that is likely to be of vascular-placental origin were prominent, including preeclampsia, retroplacental hematoma, intrauterine growth retardation and *in utero* fetal death. Complications affecting the child, including congenital abnormalities, were also observed. Only one case of hydrops fetalis was seen in the 64 pregnancies. Such high-risk pregnancies make follow-up in a maternity department mandatory, with a high level of care and regular ultrasound assessment, including Doppler evaluation, in order to detect congenital abnormalities and to follow placental and fetal development. Maternal hemoglobin must be closely monitored. Our study does not allow us to define a precise threshold, but it is likely that, as reported for women with thalassemia major, hemoglobin must be kept above 10 g/dL.[6-7] Periconceptional use of low-dose aspirin, up to 37 weeks of gestation, appears to be highly advisable in order to prevent vascular-placental complications when a previous complicated pregnancy has occurred,[8] and might be suggested in all cases.

From the reported data, we did not find any obvious correlation between pregnancy outcome and the therapeutic response before pregnancy or the presence of *RPS19* mutation in the mother. As expected, treatment-free patients were more likely to experience a pregnancy, but the proportion of complicated pregnancies was the same whether or not the women were receiving treatment. Like Alter,[5] we found no obvious impact of the affected status of the child on pregnancy outcome. Lastly, our data are at odds with a reported beneficial effect of pregnancy and lactation on the course of the disease in two cases of DBA,[9-10] since transfusion or steroid requirements were increased or stable during pregnancy. These retrospective data show that such pregnancies are high-risk and require specific follow-up involving well-trained hematologic and obstetric groups. Improvement in chelation therapy will now allow more pregnancies in women with DBA. Prospective multicenter studies, including studies on placental histology and precise description of the phenotype (clinical, hematologic and eADA status) and genotype in any child born to a DBA-affected mother, are now essential to define pregnancy outcome in this setting and to assess the benefits of systematic prevention using low-dose aspirin.

LF, TL and GT designed the study, wrote the manuscript and included patients; LDC performed molecular biology study and wrote the manuscript; IM collected data for the French registry; JM, CCN collected data for the German registry and included patients. The authors reported no potential conflicts of interest. The authors thank INSERM, the Association Française contre les Myopathies (AFM), the Ministère de la Recherche (contrat RD:4MR09F), the DBA Foundation, the Maria Daniela Arturi Foundation and the Association Française des Malades atteints de Blackfan-Diamond (AFMBD) for their support. This work was partially supported by NIH grant no. 1R01HL079565-01 NARLA M.

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