

# Outcome of Pregnancy and Disease Course among Women with Aplastic Anemia Treated with Immunosuppression

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**Background:** Aplastic anemia may develop during pregnancy and sometimes improves spontaneously after delivery. The effects of pregnancy on aplastic anemia after immunosuppressive treatment and of aplastic anemia on the outcome of pregnancy have not been described.

**Objective:** To determine the outcome of pregnancy and the disease course among women with aplastic anemia who received immunosuppressive therapy.

**Design:** Retrospective multicenter study.

**Setting:** Twelve centers participating in the European Group for Blood and Marrow Transplantation.

**Patients:** 36 women who received immunosuppressive therapy to treat aplastic anemia.

**Measurements:** Outcomes of pregnancy and aplastic anemia and blood counts before, during, and after delivery.

**Results:** The 36 pregnancies resulted in 34 live births (one set of twins), 2 elective abortions, and 1 spontaneous abortion. Of the 36 pregnancies, 22 were uncomplicated and 14 involved medical complications. Seven pregnancies (19%) were complicated by re-

lapse of aplastic anemia, and 5 patients without relapse (14%) needed transfusions during delivery. After delivery, 3 of the 7 patients who had relapse recovered spontaneously and 3 recovered after retreatment. One patient who did not respond to treatment died of aplastic anemia. A woman with aplastic anemia and paroxysmal nocturnal hemoglobinuria had a fatal cerebral thrombosis after delivery. Women with uneventful pregnancies had better prepregnancy remission status (8 complete and 11 partial remissions) and a higher median platelet count ( $146 \times 10^9$  cells/L) than did women with complicated pregnancies (2 complete remissions, 8 partial remissions, and 4 cases of paroxysmal nocturnal hemoglobinuria; median platelet count,  $92 \times 10^9$  cells/L).

**Conclusions:** Successful pregnancy with normal outcome is possible in women with aplastic anemia previously treated with immunosuppression. Complications appear to be more likely in patients with low platelet counts and paroxysmal nocturnal hemoglobinuria-associated aplastic anemia.

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\*For a list of centers that participated in the Study of the European Group for Blood and Marrow Transplantation Severe Aplastic Anaemia Working Party, see Appendix.

**A**plastic anemia is peripheral blood pancytopenia associated with unexplained hypocellularity of the bone marrow. If the disease goes untreated, patients die of bleeding or infection. Immunosuppression is the treatment of choice in patients who are not eligible for bone marrow transplantation (1–3). Hematopoiesis usually improves gradually in patients who respond to therapy, but blood counts never completely normalize in many patients (4, 5). In contrast to patients treated with bone marrow transplantation, patients given immunosuppressive therapy experience autologous hematopoietic reconstitution and have persistent damage to the stem-cell compartment. As a consequence, these patients remain at risk for relapse of aplasia or may develop paroxysmal nocturnal hemoglobinuria, a myelodysplastic syndrome, or acute leukemia (6–8).

The first case of aplastic anemia described in the literature occurred in a pregnant woman (9). Numerous case reports of aplastic anemia during pregnancy have since followed (10–14). However, the relationship between aplastic anemia and pregnancy remains unclear. It has been suggested that pregnancy causes aplastic anemia, since aplasia may remit spontaneously after abortion or delivery (15–17) and preexisting marrow insufficiency may worsen during pregnancy (18, 19). The effect of pregnancy on the disease after immunosuppressive treatment is poorly understood, but concern about relapse during pregnancy is justified.

Recurrent episodes of aplastic anemia have been reported in consecutive pregnancies (20–22).

We report on the experience of the European Group for Blood and Marrow Transplantation (EBMT) Severe Aplastic Anaemia Working Party with outcome of pregnancy and disease course among women with aplastic anemia who previously received immunosuppressive therapy.

## METHODS

### Data Collection

European centers participating in the EBMT that specialize in the treatment of aplastic anemia were asked to provide information on all women with aplastic anemia who had become pregnant after immunosuppressive treatment. Twelve centers with experience in the treatment of aplastic anemia that were involved in the long-term follow-up of these patients and were members of the Severe Aplastic Anaemia Working Party of the EBMT participated (Appendix). We sent a questionnaire to the centers that requested details on pregnancy outcomes, including early spontaneous abortions and deliberate termination, and the course of aplastic anemia during pregnancy. We contacted centers to obtain missing data. We also collected demographic information, pretreatment blood values, type and date of first-line immunosuppressive therapy, response

to treatment, and type and date of clonal complications. Obstetric data included the number of pregnancies, abortions, and deliveries; the method of delivery; complications during pregnancy, at delivery, and after delivery; and maternal and fetal outcomes. Blood counts were collected before pregnancy, at least once per trimester, and once 1 to 6 months after delivery. In most cases, blood counts of the children at delivery were not available. Patients were followed through 15 January 2000.

### Data Evaluation and Definitions

We collected data on all pregnancies reported by the centers but analyzed first and subsequent pregnancies separately. We obtained information on pregnancy outcomes and complications observed during pregnancy, at delivery, and immediately after delivery for the first observed pregnancy. Information was also requested on the postnatal development of the infants. We compared women who had complicated pregnancies with those who experienced no complications. Blood counts of the women during and after pregnancy were compared with counts obtained before pregnancy.

Severity of aplastic anemia was defined according to the criteria of Camitta and colleagues (23) and Bacigalupo and associates (1). Complete remission was defined as a hemoglobin concentration greater than 120 g/L, a neutrophil count of  $1.5 \times 10^9$  cells/L or greater, a platelet count of  $150 \times 10^9$  cells/L or greater, and no need for transfusion. Patients who did not fulfill the hematologic criteria for complete remission but did not require transfusion and had no evidence of paroxysmal nocturnal hemoglobinuria or myelodysplastic syndrome were considered to have partial remission. Relapse of aplastic anemia was defined as a decrease in blood counts to a platelet count less than  $20 \times 10^9$  cells/L or to counts necessitating regular red blood cell or platelet transfusions. Patients who needed transfusions only during delivery and had sustained platelet counts greater than  $20 \times 10^9$  cells/L were not considered to have relapse.

Paroxysmal nocturnal hemoglobinuria was defined as a positive result on the Ham or sucrose test; presence of glycosyl phosphatidylinositol-anchored protein deficiency; and typical clinical symptoms of paroxysmal nocturnal hemoglobinuria, such as hemolytic crisis or history of thrombosis. Patients who had only laboratory signs of paroxysmal nocturnal hemoglobinuria (positive results on the Ham or sucrose test or glycosyl phosphatidylinositol-anchored protein deficiency) were not considered to have paroxysmal nocturnal hemoglobinuria.

### Statistical Analysis

Women with and without complicated pregnancies were compared by using the chi-square test or the Fisher exact test for categorical data and the Mann-Whitney U test for continuous unrelated variables. We evaluated blood counts of the pregnant women before pregnancy; during the first, second, and third trimesters; and 1 to 6 months

### Context

Little is known about the effects of pregnancy on aplastic anemia and vice versa.

### Contribution

This review of pregnancies in 36 women with aplastic anemia indicates that uncomplicated pregnancy is possible after immunosuppressive therapy.

Relapse of aplastic anemia, bleeding, eclampsia, and death occurred in 14 of the 36 first pregnancies.

Complications were more likely in women with thrombocytopenia or paroxysmal nocturnal hemoglobinuria and less likely in women in complete remission.

### Implications

Women with aplastic anemia can have uncomplicated pregnancies, but complications are frequent.

—The Editors

after delivery. When several measurements were available for a particular period, the lowest value was chosen. Because of heterogeneity of blood counts among patients, fluctuations during pregnancy are shown as a percentage deviation from prepregnancy values. Results are presented as the median with quartiles and confidence intervals. Differences in blood counts during various periods with initial counts were analyzed by using the Wilcoxon signed-rank test. A *P* value of 0.05 or less was considered statistically significant.

Statistical analysis was performed by using SPSS statistical software (SPSS for Windows, release 9.0, SPSS, Inc., Chicago, Illinois). The global Fisher exact test was performed by using StatXact statistical software (release 3, Cytel Software Corp., Cambridge, Massachusetts).

## RESULTS

### Patients

Thirty-six women treated with immunosuppression had at least one pregnancy. **Table 1** shows baseline characteristics at diagnosis and at first pregnancy. The median age of the participants was 20 years (range, 7 to 33 years) at diagnosis and 28 years (range, 19 to 41 years) at delivery. Women became pregnant a median of 7.2 years (range, 1.5 to 19 years) after initial immunosuppressive therapy. The median interval between pregnancy and last follow-up was 38 months (range, 4 to 149 months). Aplastic anemia was not severe in 16 patients, severe in 16 patients, and very severe (neutrophil count  $< 0.2 \times 10^9$  cells/L) in 3 patients. Information on disease severity was missing for 1 patient.

Before pregnancy, 11 women had complete remission, 21 patients had partial remission, and 4 patients had clinical paroxysmal nocturnal hemoglobinuria. The median

**Table 1. Characteristics of Women with Aplastic Anemia Who Received Immunosuppressive Therapy before Pregnancy**

Characteristic	First Pregnancy	Subsequent Pregnancies
Pregnancies, <i>n</i>	36	11
Patients, <i>n</i>	36	9*
Abortions, <i>n</i> (%)	3 (8)	1 (9)
Elective, <i>n</i>	2	0
Spontaneous, <i>n</i>	1	1
Deliveries, <i>n</i>	33	10
Vaginal, <i>n</i> (%)	18 (55)	8 (80)
Cesarean, <i>n</i> (%)	15 (45)	2 (20)
Severity of disease at first immunosuppressive therapy, <i>n</i> (%)		
Nonsevere aplastic anemia	16 (44)	3 (27)
Severe aplastic anemia	16 (44)	7 (64)
Very severe aplastic anemia	3 (9)	0
No information available	1 (3)	1 (9)
Type of first immunosuppressive therapy, <i>n</i> (%)		
Antithymocyte globulin-containing regimen	30 (83)	8 (73)
Cyclosporine alone	1 (3)	0
Other agent	5 (14)	3 (27)
Blood values before pregnancy		
Median hemoglobin concentration (range), g/L	122 (47–150)	86 (75–129)
Median neutrophil count (range), $\times 10^9$ cells/L	2.5 (1.1–6.2)	1.8 (1.4–4.0)
Median platelet count (range), $\times 10^9$ cells/L	140 (20–294)	233 (48–282)
Remission status before pregnancy, <i>n</i> (%)		
Complete	11 (31)	2 (18)
Partial	21 (58)	9 (82)
Paroxysmal nocturnal hemoglobinuria	4 (11)	0
Median age (range), y		
At first-line immunosuppressive therapy	20 (7–33)	20 (9–25)
At pregnancy	28 (19–41)	29 (24–35)
Median interval between first-line immunosuppressive therapy and pregnancy (range), y	7.2 (1.5–19)	8.7 (3.5–22)
Median interval between pregnancy and last follow-up (range), mo	38 (4–149)	44 (7–125)

\* One woman had three subsequent pregnancies after her first pregnancy.

hemoglobin concentration before pregnancy was 122 g/L (range, 47 to 150 g/L), the median neutrophil count was  $2.5 \times 10^9$  cells/L (range, 1.1 to  $6.2 \times 10^9$  cells/L), and the median platelet count was  $140 \times 10^9$  cells/L (range, 20 to  $294 \times 10^9$  cells/L). Two patients with paroxysmal nocturnal hemoglobinuria (patients 9 and 17) required red blood cell transfusion. One patient with paroxysmal nocturnal hemoglobinuria (patient 3) had a low platelet count ( $20 \times 10^9$  cells/L) and was classified as not in hematologic remission. The fourth patient with paroxysmal nocturnal hemoglobinuria (patient 36) was assigned to the paroxysmal nocturnal hemoglobinuria group even though she met the criteria for partial remission.

Three patients in partial remission (patients 1, 19, and 22) received cyclosporine, and one patient with paroxysmal nocturnal hemoglobinuria (patient 9) received corticosteroids. One patient with paroxysmal nocturnal hemoglobinuria (patient 36) received prophylactic anticoagulation with low-molecular-weight heparin during pregnancy and after delivery.

### Pregnancy Outcomes

The 36 first pregnancies resulted in 34 live births (one set of twins), 2 elective abortions, and 1 spontaneous abortion. There were 18 vaginal deliveries (54% [95% CI, 36% to 72%]) and 15 deliveries by cesarean section (46% [95% CI, 28% to 64%]). The course of pregnancy was uneventful for the mother and the child in 19 of the 36 pregnan-

cies (53% [95% CI, 35% to 70%]), including the twin pregnancy.

Seventeen pregnancies (47% [95% CI, 30% to 65%]) involved a complication in the mother ( $n = 11$ ), the child ( $n = 3$ ), or both ( $n = 3$ ). Five children were born 2 to 4 weeks prematurely. Three of the five premature births occurred in women who had had relapse or developed progressive thrombocytopenia, and one occurred in a woman receiving cyclosporine during pregnancy. One of the premature infants (born to patient 3) had neonatal allo-immune thrombocytopenia (Table 2). One spontaneous abortion occurred in a woman who had four pregnancies (patient 12).

Birthweight was reported in 28 of the 34 evaluable patients. This information was not applicable for the three pregnancies that terminated with abortion. The median birthweight was 3.1 kg (range, 1.84 to 4.0 kg). No child died after delivery, and postnatal development was reported as normal in all infants who were born alive.

Figure 1 shows the type and sequence of pregnancy-related complications. Two cases of eclampsia occurred, one in a woman who had clinical paroxysmal nocturnal hemoglobinuria before pregnancy (patient 36) and one in a woman who had relapse of aplastic anemia and therefore received retreatment with antithymocyte globulin during the last trimester of her pregnancy (patient 20). Both of these patients delivered healthy infants by cesarean section

and recovered from eclampsia after delivery. The patient with paroxysmal nocturnal hemoglobinuria (patient 36) was subsequently treated with warfarin. Patients 3 and 26 presented with excessive postdelivery bleeding after successful cesarean section. In both cases, bleeding was associated with severe thrombocytopenia, and the two patients had received platelet transfusions during delivery.

### Outcome of Aplastic Anemia

Seven of the 36 pregnancies (19% [95% CI, 8% to 36%]) were complicated by relapse of aplastic anemia, characterized mainly by a decrease in erythrocyte and platelet counts that necessitated transfusion. During the second and third trimesters, the 7 patients with relapse had platelet counts less than  $20 \times 10^9$  cells/L and hemoglobin concentrations less than 100 g/L. However, neutrophil counts were less than  $0.5 \times 10^9$  cells/L in only 1 of the 7 patients.

Before pregnancy, 2 of the 7 patients with relapse (patients 6 and 20) had complete remission, 4 had partial remission (patients 8, 26, 28, and 34), and 1 had clinical paroxysmal nocturnal hemoglobinuria with severe thrombocytopenia (patient 9) (Table 3). After delivery, 6 of the 7 patients with relapse recovered, 3 of them spontaneously within 1 to 3 months and 3 after retreatment with antithymocyte globulin (patient 6), cyclosporine (patient 26), or corticosteroids (patient 34). Patient 6 developed staphylo-

**Table 2. Complications Affecting Infants during Patients' First Pregnancy**

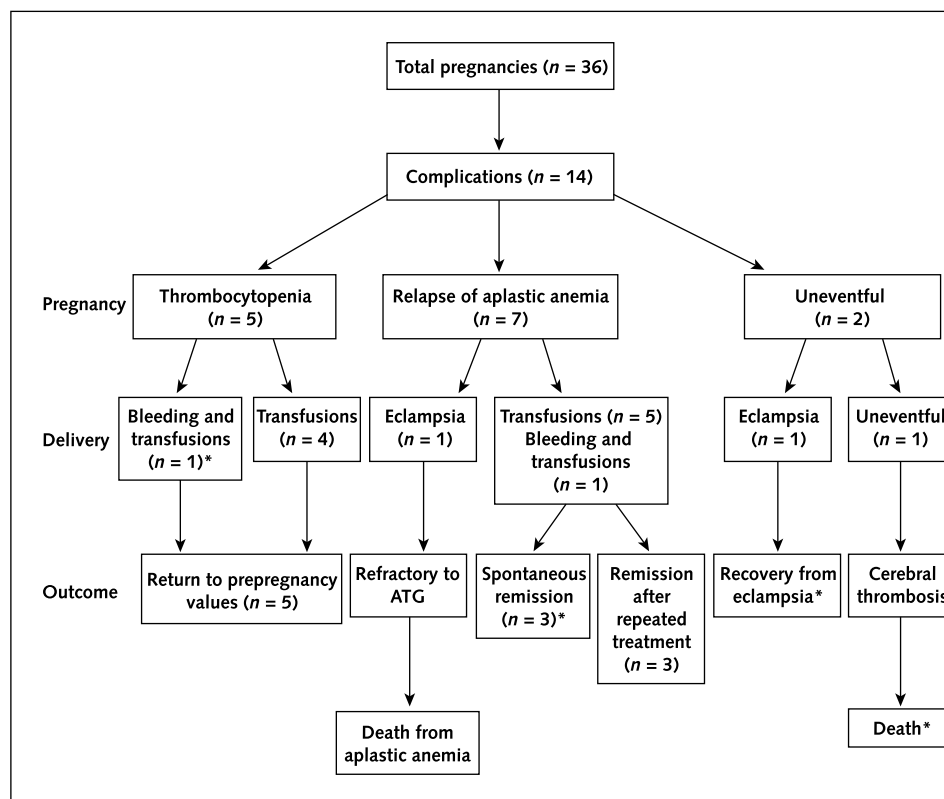
Patient	Event in the Infant	Event in the Mother
1	Premature birth (2 weeks)	Cyclosporine therapy continued during pregnancy
3	Premature birth, neonatal alloimmune thrombocytopenia*	Thrombocytopenia with clinically significant postpartum bleeding, clinical paroxysmal nocturnal hemoglobinuria
6	Premature birth (4 weeks)	Relapse of aplastic anemia
12	Spontaneous abortion	Uneventful
24	Premature birth (4 weeks)	Uneventful
26	Premature birth (4 weeks)	Relapse of aplastic anemia

\* Not related to aplastic anemia.

coccal lung abscesses but recovered after treatment with antibiotics. Patient 20 did not respond to retreatment with antithymocyte globulin.

In addition to these seven patients who had relapse, five patients (14% [95% CI, 5% to 30%]) became progressively thrombocytopenic during pregnancy. Four of these five patients did not fulfill the criteria for relapse of aplastic anemia. The fifth woman (patient 3) was not considered to have relapse because she was not in remission before pregnancy. All five women required red blood cell and platelet

**Figure 1. Complications in participants during first pregnancy, at delivery, and after delivery.**



The outcome of 11 subsequent pregnancies in 9 women are not shown. Numbers in parentheses are numbers of patients. ATG = antithymocyte globulin. \*Indicates patients who had paroxysmal nocturnal hemoglobinuria before conception. This applies to only 1 of the 3 patients with spontaneous remission.

Table 3. Complications in the Mother during First Pregnancy and Delivery\*

Patient	Before Pregnancy		At Delivery					
	Clinical Status	Platelet Count	Clinical Status	Hemoglobin Concentration	Neutrophil Count	Platelet Count	Type of Delivery	Red Blood Cell Transfusion/Platelet Transfusion
		$\times 10^9$ cells/L		g/L		$\times 10^9$ cells/L		
3	PNH	20	Thrombocytopenia	74	1.8	15	Cesarean	Yes/Yes
6	Complete remission	151	Relapse	86	0.3	14	Cesarean	Yes/Yes
8	Partial remission	63	Relapse	65	4.0	12	Vaginal	Yes/Yes
9	PNH†	45	Relapse	48	1.2	15	Vaginal	Yes/No
14	Partial remission	92	Thrombocytopenia	79	2.7	59	Cesarean	No/No
17	PNH†	134	PNH	92	2.9	65	Cesarean	Yes/No
19	Partial remission	75	Thrombocytopenia	100	2.4	33	Cesarean	No/No
20	Complete remission	215	Relapse	80	2.4	15	Cesarean	Yes/Yes
26	Partial remission	71	Relapse	98	2.4	11	Cesarean	Yes/Yes
28	Partial remission	NA	Relapse	NA	NA	NA	Cesarean	Yes/Yes
29	Partial remission	51	Thrombocytopenia	119	0.9	33	Cesarean	No/No
32	Partial remission	150	Thrombocytopenia	120	4.0	90	Cesarean	No/No
34	Partial remission	134	Relapse	81	2.5	11	Cesarean	Yes/Yes
36	PNH	97	Stable PNH	NA	2.4	88	Cesarean	No/No

\* ATG = antithymocyte globulin; PNH = paroxysmal nocturnal hemoglobinuria.  
† Regular transfusions of red blood cells before pregnancy.

transfusions at delivery. After delivery, blood counts returned to prepregnancy values in all patients.

Two deaths occurred after pregnancy. One of the patients with relapse who was retreated with antithymocyte globulin (patient 20) died of refractory disease 1 year after delivery. Patient 17 died approximately 1 month after delivery. She had paroxysmal nocturnal hemoglobinuria before conception but had an uncomplicated pregnancy and delivery. Seventeen days after delivery, the patient developed bacterial cystitis, and 7 days later, she died of cerebral thrombosis.

The four patients with clinical paroxysmal nocturnal hemoglobinuria had complicated courses, including relapse of aplastic anemia (patient 9), increased transfusion dependency (patient 3), death due to cerebral thrombosis 1 month after delivery (patient 17), and eclampsia (patient 36). Three women were receiving cyclosporine when pregnancy was detected. One of them (patient 19) stopped treatment and developed progressive thrombocytopenia that required platelet transfusions at delivery. The other two patients (patients 1 and 22) continued the treatment throughout pregnancy. Both had a decrease in their platelet counts but did not become transfusion dependent. In addition, patient 34 received cyclosporine during the third trimester to treat relapse of aplastic anemia. None of the three infants born to mothers who took cyclosporine during pregnancy had physical deformity at birth.

### Pregnancy with and without Complications

We compared the 19 pregnancies with an uneventful maternal course and the 14 complicated pregnancies (Table 4). The two groups differed in prepregnancy characteristics and pregnancy outcomes. Before pregnancy, the patients without complications had better remission status (8

in complete remission [42%], 11 in partial remission [58%], and no cases of paroxysmal nocturnal hemoglobinuria) and higher median platelet counts ( $146 \times 10^9$  cells/L [range, 48 to  $294 \times 10^9$  cells/L]) than did women with complications (2 in complete remission [14%], 8 in partial remission [57%], and 4 with paroxysmal nocturnal hemoglobinuria [29%]; median platelet counts,  $92 \times 10^9$  cells/L [range, 20 to  $215 \times 10^9$  cells/L];  $P < 0.05$ ). In contrast, age at first immunosuppressive therapy and at delivery, interval between immunosuppression and pregnancy, and hemoglobin and neutrophil counts did not differ between the two groups. Only 3 of 19 (16% [95% CI, 3% to 40%]) uneventful pregnancies required cesarean section, compared with 12 of 14 (86% [95% CI, 57% to 98%]) complicated pregnancies ( $P < 0.001$ ). In many cases, the reason for cesarean section was not specified. However, at delivery, 6 women with cesarean section had platelet counts less than  $50 \times 10^9$  cells/L and 7 women had counts of 50 to  $100 \times 10^9$  cells/L. The median birthweight was significantly higher in women with uneventful pregnancies than in those with complicated pregnancies (3.3 kg [range, 2.5 to 3.9 kg] vs. 2.5 kg [range, 1.8 to 4.0 kg];  $P = 0.003$ ). Neutrophil and platelet counts ( $P = 0.001$ ) but not hemoglobin concentration ( $P = 0.17$ ) at delivery were significantly higher in women without complications (Table 4).

### Changes in Blood Counts during Pregnancy

During pregnancy, the median hemoglobin value was 91% (75% CI, 85% to 100%;  $P = 0.01$ ) of the prepregnancy value in the first trimester, 81% (75% CI, 75% to 81%;  $P = 0.001$ ) in the second trimester, and 81% (75% CI, 70% to 90%;  $P = 0.001$ ) in the third trimester. After pregnancy, hemoglobin concentrations returned to prepregnancy values (97% [75% CI, 90% to 105%];

Table 3—Continued

Problems and Follow-up
Excessive postpartum bleeding; return to prepregnancy blood counts
Premature birth, lung abscess, and remission after ATG therapy
Spontaneous remission
Spontaneous remission
Perioperative transfusions, return to prepregnancy blood counts
Cerebral thrombosis 1 month after delivery, death
Perioperative transfusions, return to prepregnancy blood counts
Eclampsia, refractory to ATG therapy, death 1 year after delivery
Excessive postpartum bleeding, remission after steroid therapy
Spontaneous remission
Return to prepregnancy blood counts
Perioperative platelet transfusions; return to prepregnancy blood counts
Premature birth, remission after treatment with cyclosporine
Eclampsia, return to prepregnancy blood counts, PNH

$P > 0.2$ ) (Figure 2, top). Neutrophil counts increased compared with prepregnancy counts during the first (median, 145% [75% CI, 112% to 171%];  $P = 0.001$ ), second (median, 136% [75% CI, 97% to 223%];  $P = 0.002$ ), and third trimesters (median, 152% [75% CI, 88% to 200%];  $P = 0.002$ ) and returned to prepregnancy values after delivery (median, 100% [75% CI, 81% to 159%];  $P > 0.2$ ) (Figure 2, middle). In contrast, the median platelet count was 80% (75% CI, 70% to 101%;  $P = 0.067$ ) of prepregnancy values in the first trimester, 70% (75% CI, 45% to 88%;  $P = 0.004$ ) in the second trimester, and 62% (75%

CI, 37% to 87%;  $P < 0.001$ ) in the third trimester. After delivery, platelet counts returned to prepregnancy values (median, 108% [75% CI, 79% to 135%];  $P > 0.2$ ) (Figure 2, bottom).

### Subsequent Pregnancies

Nine of the 36 patients had 11 additional pregnancies. Eight women had one additional pregnancy, and 1 woman (patient 12) had three additional pregnancies. Table 1 shows the characteristics of these 11 pregnancies. Seven of the 11 pregnancies (55% [95% CI, 25% to 83%]) were uncomplicated. Of the remaining 4 pregnancies, 1 involved premature birth of an infant with ureteral atresia (patient 32). Two other complicated pregnancies occurred in patient 12, who had four observed pregnancies. She experienced two spontaneous abortions (first and second pregnancy) and one intrauterine death (third pregnancy) and delivered one healthy child (fourth pregnancy). One year after the patient's last pregnancy, rheumatoid arthritis was diagnosed. Laboratory tests for antiphospholipid antibody were not available.

Of the nine women with subsequent pregnancies, only one had disease-related complications (patient 29). This woman experienced relapse during the third trimester but underwent spontaneous remission after pregnancy. During her first pregnancy, her platelet counts decreased to  $33 \times 10^9$  cells/L, but she recovered without treatment at the end of pregnancy.

### DISCUSSION

Our data suggest that successful pregnancy is possible after treatment of aplastic anemia with immunosuppression. More than 50% of the pregnancies were uneventful.

Table 4. Prepregnancy Characteristics and Outcome of Pregnancy in Women with and without Maternal Complications\*

Characteristic	Women without Complications (n = 19)	Women with Complications (n = 14)	P Value
Age at immunosuppression, y	21 (7–27)	20 (10–30)	>0.2†
Age at pregnancy, y	28 (22–39)	29 (20–35)	>0.2†
Interval between immunosuppression and pregnancy, y	7.7 (1.5–19)	7.8 (1.7–19)	>0.2†
Delivery by cesarean section, n (%)	3 (16)	12 (86)	<0.001‡
Birthweight, kg	3.3 (2.5–3.9)	2.5 (1.8–4.0)	0.003†
Prepregnancy disease status, n (%)§			
Complete remission	8 (42 [20–66])	2 (14 [2–43])	0.0248
Partial remission	11 (58 [33–80])	8 (57 [29–82])	
Paroxysmal nocturnal hemoglobinuria	0	4 (29 [8–58])	
Blood values			
Before pregnancy			
Hemoglobin concentration, g/L	127 (80–150)	114 (47–132)	0.13†
Neutrophil count, $\times 10^9$ cells/L	2.5 (1.4–6.2)	2.4 (1.1–3.5)	>0.2†
Platelet count, $\times 10^9$ cells/L	146 (48–294)	92 (20–215)	0.037†
At delivery			
Hemoglobin concentration, g/L	96 (68–124)	83 (48–120)	0.17†
Neutrophil count, $\times 10^9$ cells/L	4.6 (3.0–7.9)	2.4 (0.3–4.0)	<0.001†
Platelet count, $\times 10^9$ cells/L	99 (45–278)	19 (11–90)	<0.001†

\* Data are presented as the median (range) or number (percentage) of patients.

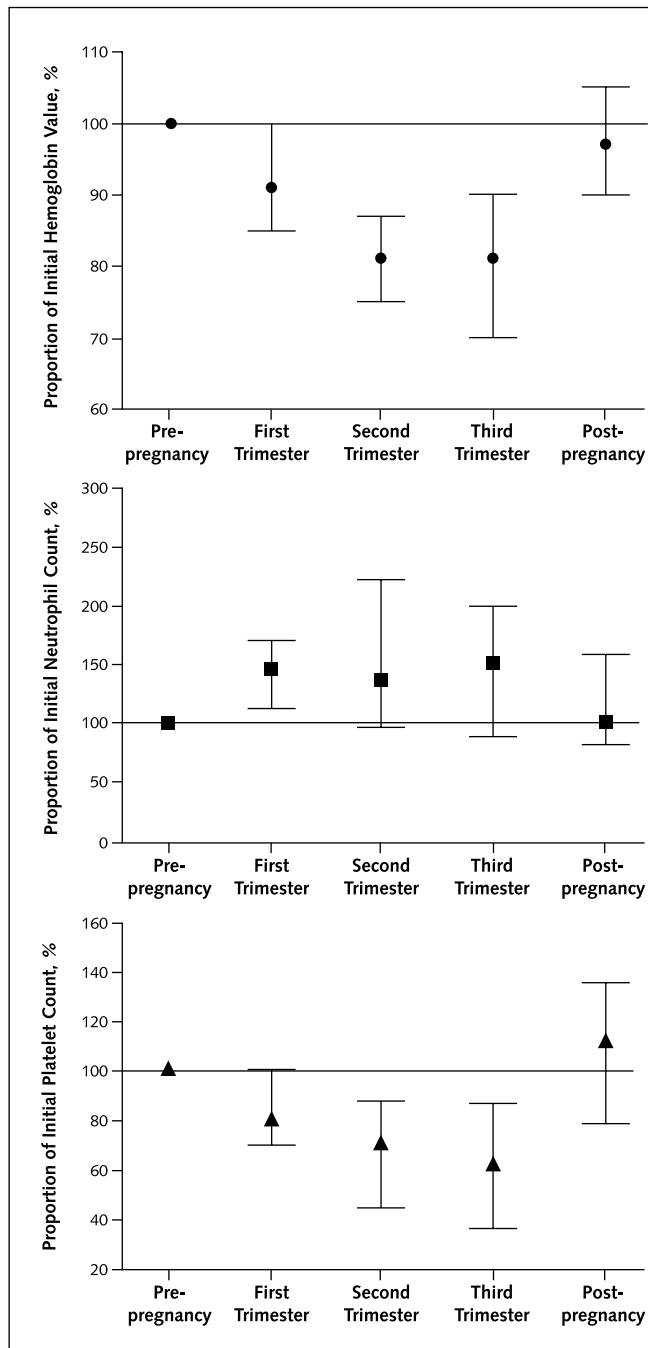
† Mann-Whitney U test.

‡ Chi-square test.

§ Numbers in square brackets are 95% CIs.

|| Fisher exact test.

**Figure 2. Hemoglobin concentration and neutrophil and platelet counts before, during, and after first pregnancy.**



**Top.** Hemoglobin concentration. **Middle.** Neutrophil count. **Bottom.** Platelet count. Bars represent 75% CIs.

Nevertheless, complications in the mothers and infants were common and were often related to the aplastic anemia. One third of the patients became transfusion dependent during pregnancy, and 19% experienced relapse of aplastic anemia. In most cases, women with relapsed aplastic anemia or progressive thrombocytopenia during pregnancy had cesarean section. Most patients with relapse recovered spontaneously or after repeated immuno-

suppressive therapy. We observed two deaths that were possibly related to pregnancy.

Information about factors associated with adverse pregnancy outcome would be helpful for patient counseling. We have shown that women whose disease is in remission before conception and those with normal platelet counts are more likely than those with persistent cytopenias to have an uneventful pregnancy. However, normal blood counts before conception do not guarantee that relapse of aplastic anemia will not occur. Two of the seven relapses occurred in patients who were in complete remission before pregnancy, and one of these patients eventually died of refractory disease.

We observed no decrease in blood counts or relapse during pregnancies that ended in abortion. This observation is not surprising, since most relapses occurred during the second and third trimesters. The course of the four pregnancies in women with clinical paroxysmal nocturnal hemoglobinuria was particularly dramatic: These patients experienced such complications as transfusion dependence, relapse of aplastic anemia, eclampsia, and postdelivery death.

Patient age at the time of first treatment or during pregnancy was not associated with adverse outcome. Cesarean section was most frequent in women with relapse of aplastic anemia or symptomatic thrombocytopenia, and infant birthweights in these women were significantly lower. Second pregnancies had fewer maternal complications, possibly because women with an uncomplicated pregnancy were more likely to become pregnant again.

Relapse after immunosuppression is common. In a retrospective study of the EBMT, the actuarial risk for relapse was 35% at 14 years (7). Therefore, the question of whether the incidence of relapse during pregnancy is higher than expected is valid. The relapse incidence curve after immunosuppression appears to follow a zero-order kinetic; that is, relapse does not occur more frequently early after treatment than late after treatment. Therefore, extrapolating from the data of the EBMT, the probability of relapse during 9 months should be lower than 2%. Thus, the 19% relapse rate observed during the second and third trimesters was probably related to pregnancy. Furthermore, the high proportion of spontaneous remission that we observed at the end of pregnancy is unique in the reported clinical experience of patients with aplastic anemia. Hence, our study provides additional evidence of an etiologic relationship between pregnancy and aplastic anemia.

Some patients with aplastic anemia are dependent on cyclosporine and experience severe thrombocytopenia or relapse of aplastic anemia if treatment is discontinued (3). Data from renal transplantation studies show that cyclosporine does not increase the risk for congenital malformations (24–27). In our series, two patients received cyclosporine during pregnancy and delivered normal infants. Thus, our data support treatment continuation.

We did not investigate the ability of women with aplastic anemia to become pregnant. However, there is no theoretical reason why infertility would occur in women previously treated with immunosuppression. In contrast, pregnancies in women after bone marrow transplantation are rare and depend mainly on the intensity of the conditioning regimen used (28).

Blood counts changed significantly during pregnancy and tended to return toward prepregnancy values within 1 to 6 months after delivery. Hemoglobin and platelet counts decrease, whereas neutrophil counts increase during pregnancy in women who have previously been treated for aplastic anemia. In healthy women, platelet counts decrease by 11% in uncomplicated pregnancy, mainly because of a dilution effect, but usually remain within the normal range. Only about 8% of women develop a moderate incidental thrombocytopenia (29–32). During uncomplicated pregnancy, neutrophil counts tend to double (33, 34). It is not clear why pregnancy would modify the blood counts of patients with aplastic anemia and affect the natural course of this disease. Hormonal changes, altered immunity during pregnancy, and a decreased marrow reserve further drawn by the demands are possible explanations that merit investigation.

Our study is limited by its retrospective design. Nonetheless, the data provide the best current information for counseling women with aplastic anemia who are contemplating pregnancy. Little is known about the long-term health of children born to women with aplastic anemia, but we observed no problems at birth. Uncomplicated pregnancy is possible, but a risk for complications exists that appears to be greater in patients with low platelet counts and paroxysmal nocturnal hemoglobinuria. The complicated course of pregnancies in patients with paroxysmal nocturnal hemoglobinuria suggests that routine prophylactic anticoagulation during pregnancy and the postpartum period should be considered.

## APPENDIX

The following centers participated in the Study of the Working Party on Severe Aplastic Anaemia of the European Group for Blood and Marrow Transplantation: University Hospitals, Basel, Switzerland (EBMT no. 202); University Hospital, Ulm, Germany (EBMT no. 204); Hôpital St. Louis, Paris, France (EBMT no. 207); Hospital Clinic, Barcelona, Spain (EBMT no. 214); Ospedale San Martino, Genoa, Italy (EBMT no. 217); St. James Hospital, Trinity College, Dublin, Ireland (EBMT no. 257); University Hospital, Innsbruck, Austria (EBMT no. 271); University Hospital, Patras, Greece (EBMT no. 281); Avon Haematology Unit, Bristol Haematology and Oncology Center, Bristol, United Kingdom (EBMT no. 386); Leiden University Medical Center, Leiden, the Netherlands (EBMT no. 398); St. George's Hospital, London, United Kingdom (EBMT no. 539); Dr.-Horst-Schmidt-Kliniken, for the German SAA-Study, Wiesbaden, Germany (EBMT no. 586).

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