Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 632–635

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Long-term outcome of pregnancy complicating with severe aplastic anemia under supportive care

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ARTICLE INFO

Article history:
Accepted 17 August 2016

Keywords:
Aplastic anemia
Pregnancy
Morbidity

ABSTRACT

Objectives: Pregnancy associated with aplastic anemia (AA) is a rare and heterogeneous disorder. We aimed to identify and evaluate the maternal and pregnant outcomes of pregnancy-associated severe AA treated with supportive care.

Materials and methods: A 25-year retrospective study was conducted at in a single center between 1990 and 2014 with pregnancy associated severe AA. In addition, relevant published cases of antenatally diagnosed pregnancy-associated severe AA after 1990 were identified by PubMed. The main goal was to determine the impact of various risk factors on maternal and fetal outcomes.

Results: 15 women with 18 pregnancies were enrolled. With addition of the published reports in literature, a total of 36 cases were included for reference review. Univariate analysis showed that low platelet counts (<2.0 × 10^9/L), bone marrow hypocellularity (<25%), and late diagnosis during pregnancy were predictors of poor maternal outcomes ($P < 0.05$). The complication rate of pregnancy outcomes was 53.3%, including preterm delivery, small gestational age (SGA), preterm premature ruptured of membranes (PPROM) and preeclampsia.

Conclusions: This study identified the risk factors of mortality and morbidity in pregnant women with severe AA, as well as the obstetrical complications associated with neonatal outcome.

Introduction

Aplastic anemia is a rare and potentially life-threatening disorder, especially for women during pregnancy [1,2]. Aplastic anemia can be either acquired or congenital. The inciting factors of acquired AA include radiation, drugs, infection and organic compounds. Some studies proposed the hypothesis indicating that pregnancy is a risk factor; however the exact pathophysiology between pregnancy and AA is still controversial [3–5]. The risk to pregnant women is focused on hemorrhage and uncontrolled sepsis due to pancytopenia. The true mechanism and pathophysiology of AA is still unclear [2], but it is generally considered as an autoimmune disorder [1]. Immunosuppressive agents or hematopoietic stem cell transplantation are contraindicated during pregnancy because the potential toxicity to fetus [3,5]. Supportive care is the mainstay of treatment in pregnancy, and the prognosis is better than it was several decades ago, largely because of better supply of blood products [5]. Meanwhile, the fetus would also suffer from high risk of preterm delivery, growth restriction or intrauterine fetal death as a consequences resulted from maternal morbidity [6]. Thus, a pregnancy complicated by severe AA is a great challenge for obstetricians.

The present study summarized the data on prenatal and postnatal conditions of 15 cases of pregnant women and 18 pregnancies which with the diagnosed of pregnancy-associated severe AA. By pooling our data with a review of published cases, we aimed to evaluate outcome of pregnancy-associated severe AA and investigated the factors that could be associated with poor maternal outcomes during and after pregnancy.

Materials and methods

A retrospective study was conducted by compiling all patients between 1990 and 2014. Fifteen cases were diagnosed and received treatment as pregnancy-associated aplastic anemia in the

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http://dx.doi.org/10.1016/j.tjog.2017.08.010

Department of Obstetrics and Gynecology, Chang Gung Memorial hospital. Cases that had ongoing disease during pregnancy and received abortions were excluded. There were no inciting factors such as infection, irradiation, leukemia and immunological disorders in these cases [7]. We reviewed the characteristics included age, parity, delivery (gestational age and mode), baseline hematocrit, complications of pregnancy. The diagnosis of pregnancy-associated severe AA was made according to the diagnostic criteria proposed by Brodsky et al. [1]. Severe aplastic anemia was diagnosed as bone marrow biopsy showing less than 25 percent of normal cellularity or less than 50 percent normal cellularity in which fewer than 30 percent of the cells are hematopoietic and at least two of the following are present: absolute reticulocyte count below 40,000/microliter; absolute neutrophil count (ANC) less than 500/microliter; or platelet count below 20,000/microliter [8]. Bone marrow aspiration was done in each woman in present study.

To make definite diagnosis of aplastic anemia, other etiologies of cytopenias, such as paroxysmal nocturnal hemoglobinuria (PNH), large granular lymphocyte leukemia, myelodysplastic syndromes (MDS), marrow replacement by fibrosis or tumor, severe megaloblastic anemia, acute leukemias, and overwhelming infection due to HIV or the viral hemophagocytic syndrome were excluded carefully by bone marrow biopsies and clinical manifestations.

Seven of the 15 cases had a known history of severe AA and 8 cases were diagnosed severe AA during prenatal clinic, underwent visits at every one to two-week interval based upon the severity of clinical manifestations. Steroids were used while blood transfusion with leukocyte-free PRBC and platelets were given during prenatal period to maintain the hemoglobulin level higher than 8 g/dL and platelet counts greater than 20×10^9/L. Clinical data and obstetric surveillance decided the timing and mode of delivery. After delivery, the patients underwent postpartum care at every 2 weeks in the first 2 months. Complete remission (CR) was defined as neutrophil counts greater than 2.0×10^9/L and platelet counts greater than 100×10^9/L. Partial remission (PR) was defined as neutrophil counts higher than 1.0×10^9/L and platelet count greater than 30×10^9/L. Non-responder (NR) was defined as patients who required blood transfusion to maintain the neutrophils and platelet counts [9].

Detailed follow-up information on each case was obtained in all instances through medical records and/or telephone interviews with the physicians.

Statistics

The results were shown as percentages for frequencies, and as means for variables. The data were analyzed using the SPSS 12.0 statistical package (Chicago, IL, USA). Fisher's exact test was used to evaluate the significance of differences between designated groups. $P < 0.05$ was considered statistically significant.

Results

The demographics of the 15 cases of pregnancy-associated aplastic anemia from our hospital were shown in Table 1. The maternal and neonatal outcomes were presented in Table 2. In the 18 pregnancies, one case suffered from preterm premature ruptured of membranes at 22nd weeks of gestational age and had to terminate the pregnancy due to severe oligohydramnios. To analyze the complications during the 17 survival pregnancy, preterm birth (<37 weeks) was 41.2% (7/17), small gestational age was 11.8% (2/17), preeclampsia was 5.9% (1/17) and PPROM was 17.6% (7/17). 17 deliveries had babies survived without major complications (Table 3).

Of the 15 pregnant women, 3 cases died within five years after delivery, with one at 2 weeks, one at a year and one after four years later due to disease progression to myelodysplastic syndrome and uncontrolled sepsis. 9 of 12 survival cases were under status of complete remission (CR) and the other 3 cases were in partial remission (PR). The mean maternal age was 31.7 years (range 22–38). The mean follow-up period was 48.9 months (range 12–184 months) (Table 3).

In the pooled analysis which included the data from literature reports, there were 31 cases with pregnancy-associated severe AA enrolled by review of literature [3–5]. Adding our 15 cases gave a total of 46 cases. Five patients were excluded from the analysis because the detail individual outcomes of interest were not specified. Five cases were excluded due to loss follow-up. The detailed study design was summarized in Fig. 1. Thus, 36 cases were included for analysis and we categorized into two groups. The group A included 27 patients with an uneventful maternal outcomes (complete remission or partial remission) and group B included 9 complicated pregnancies (3 cases of non-responder and 6 cases of maternal death). The two groups differed in prenatal clinical courses and pregnancy outcomes.

Table 1
Clinical and hematological profile of the 18 pregnancies at presentation.

Case no.	Age (years)	Parity	GA (weeks)	Hb (g/L)	WBC ($\times 10^9$/L)	Neutrophil ($\times 10^9$/L)	PLT ($\times 10^9$/L)	BM (%)
1	29	1	9	7	3.8	1.8	29	20
2	33	1	27	3.7	3.9	2.3	15	5
3	28	1	11	7.4	3.4	1.7	14	20
	35	2	7	9	4.5	2.4	49	
4	35	2	16	7.4	2.2	0.8	11	15–20
5	24	1	22	9.3	2.7	1.8	34	25
6	22	1	18	6.5	3.1	1.0	4	20
7	38	1	26	9.9	3.4	2.0	36	30
8	31	1	36	9.3	5.0	3.3	45	30
9	28	1	21	8.4	3.9	2.4	32	15–20
	31	2	10	7.3	3.8	1.3	22	
10	34	1	13	2.1	4.9	2.8	17	20
11	31	0	35	6.7	3.8	1.8	14	25
	34	1	11	6.4	3.4	1.6	18	
12	31	1	26	4.4	3.4	1.9	8	15
13	35	0	8	10.6	4.6	2.7	29	10
14	37	1	37	9.3	5.0	3.1	45	25
15	34	0	11	6.5	2.8	1.1	12	20

Abbreviations: BM, bone marrow; GA, gestational age of diagnosis; Hb, hemoglobin; WBC, white blood cell count; PLT, platelet count.

Table 2
Clinical course and final outcome of the 18 pregnancies.

Case no.	GA	Delivery	BBW	Association problems	Neonatal outcome	Follow up	Maternal outcome
1	38	CS	2880		Alive	84	PR
2	32	CS	1760	Preeclampsia	Alive	11	Expired
3	38	CS	2922		Alive	34	PR
	38	CS	2678		Alive	23	PR
4	38	CS	2980		Alive	168	CR
5	37	CS	2240		Alive	184	PR
6	36	SD	2720		Alive	48	Expired
7	36	CS	2980		Alive	36	PR
8	36	CS	2720	PROM	Alive	42	Expired
9	37	CS	3120		Alive	36	PR
	38	CS	3460		Alive	34	PR
10	37	CS	2680		Alive	24	PR
11	36	CS	2820		Alive	18	CR
	28	CS	920/1260	PROM	Alive	36	CR
12	34	CS	2380	PROM	Alive	38	PR
13	38	CS	3920		Alive	12	CR
14	39	CS	2820		Alive	13	PR
15	22	SD	240	PROM	Expired	48	PR

Abbreviation, GA, gestational age at delivery; BBW, birth body weight; PROM, preterm premature ruptured membranes; CS, Cesarean section; SD, Spontaneous delivery; PR, Partial Remission; CR, Complete Remission.

Table 3
Summary of clinical characteristics and outcomes in 18 pregnancies.

Mean maternal age (years)	31.7 (range 22–38)
Survival of pregnancy outcome	17/18 pregnancies
Complication of pregnancy	8/15
Preterm delivery (GA <37th weeks)	7
Hypertension/Preeclampsia	1
Small gestational age	2
PPROM	3
Duration of follow up after delivery (months)	48.9 (range 6–184)
Mean gestational age at delivery (weeks)	34.2 (range 28–40)
Mean new born weight (gm)	2591 (range 920–3920)
Pre-pregnant diagnosed	7/15

The data was presented by mean (range).

Low platelet counts, late disease presentation and low bone marrow cellularity were significant different between the two groups. The platelet counts were significant lower in complicated group ($P < 0.05$), and bone marrow cellularity was also lower in complicated group ($P < 0.05$). Moreover, the later the AA disease presents during gestation, the worse the maternal outcome ($P < 0.05$). The maternal age, gestational age at diagnosis, hemoglobin count, absolute neutrophil count, and fetal birth body weight show no significant different between Group A and Group B (Table 4).

Discussion

Pregnancy associated severe AA is a rare but life-threatening disorder. Although the true etiology of aplastic anemia is uncertain, pregnancy was thought to be a major risk factor of aplastic anemia since the Ehritch et al. [4] reported the first case of aplastic anemia in a pregnant woman.

The large population base studies demonstrated an incidence of acquired AA was two cases per million in Europe but the incidence seems to be two to three times higher in Southeast Asia [10,11]. These results may explain that the large case series study of pregnancy associated AA was almost reported from Asia [3–5,12]. In our hospital, 15 cases were enrolled and the incidence of pregnancy-associated anemia was about 1 in 10,000 pregnancies in our hospital. Being a tertiary medical center, this incidence may not reflect the actual incidence of pregnancy-associated AA in Taiwan, nevertheless it could provide further nationwide population study.

According to the recent successful experience of supportive management of pregnancy-associated severe AA [4,5], the pathophysiology of pregnancy-associated severe AA may be different from other acquired aplastic anemia. The trigger point was supposed as the high level of hormones during pregnancy. After delivery, the high level of sex hormone would fall to normal range and the trigger vanished. This spontaneous recovery of AA after delivery had been reported in previous studies [13–16].

During pregnancy, the level of placental lactogen, erythropoietin and estrogen are increased. Placental lactogen and erythropoietin can stimulate the function of hemopoiesis, However, increased estrogen level during pregnancy would inhibit hematopoiesis was proved in canine study [3–5,17] and many previous studies showed most AA will have spontaneous recovery after delivery [13,14,16]. The pathophysiology of acquired aplastic anemia is immune mediated in most cases [1]. The sex hormone, such as estrogen, progesterone will affect immune response had been mentioned in previous studies [18]. However, sex hormones alone do not cause autoimmune disease. Abnormal hormone levels may provide the stage for other factors (genetic, infectious) to trigger disease, such as aplastic anemia [19]. After careful review the history of our cases, all of them were adult onset and none had identifiable inciting factors.

Of our 15 cases complicated with severe AA, 9 cases had complete remission and 3 cases had partial remission. A retrospective study of 352 non-pregnant cases of acquired AA showed that the prognostic factors of AA were existence of infection, platelet count, reticulocyte count, granulocyte count and percentage of the

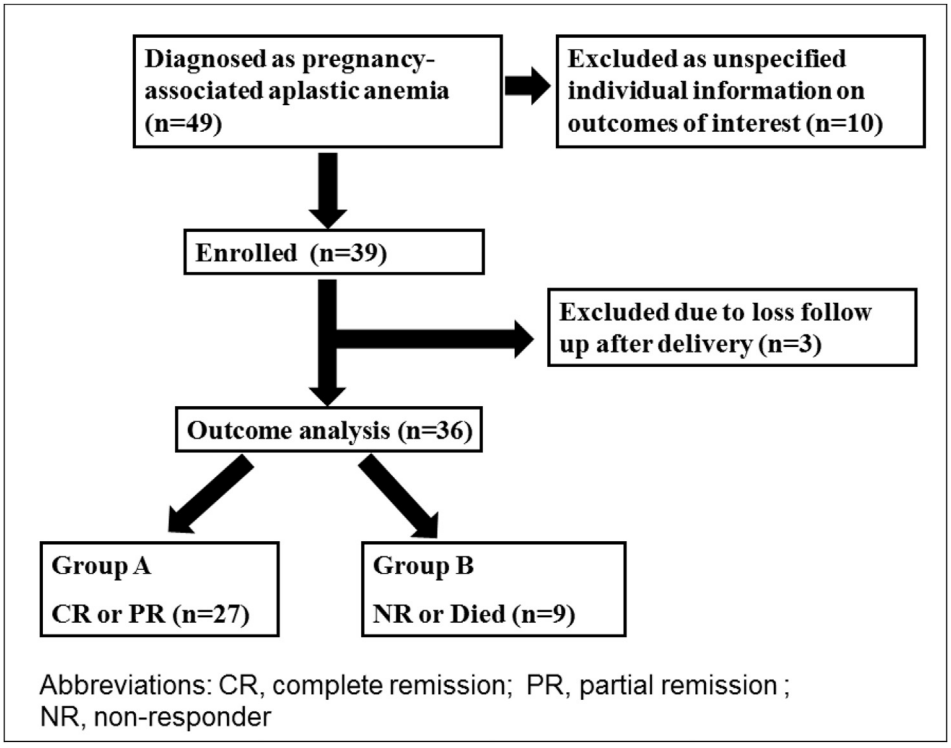

Fig. 1. Flow chart of participants in the trial.

Table 4
Pregnancy characteristics and outcome of pregnancy in women with and without remission after delivery.

	Group A (n = 27)	Group B (n = 9)	P value
Age (years)	31 (21–38)	30 (22–38)	0.87
Diagnosis (weeks)	20 (8–40)	34 (18–38)	0.03*
WBC ($\times 10^9$/L)	3.8 (2.1–5.0)	3.4 (1.1–4.9)	0.78
Hb (g/dL)	8.4 (3.0–10.6)	6.5 (3.1–9.9)	0.25
Neutrophil counts ($\times 10^9$/L)	1.8 (0.5–3.3)	1.9 (0.2–3.2)	0.95
Platelet counts ($\times 10^9$/L)	3.4 (1.4–8.0)	1.0 (0.4–4.7)	0.04*
BM cellularity <25%	14/25	6/7	0.01*
Birth weight (gm)	2800 (150–3920)	2800 (1340–3900)	0.86

Group A, Complete remission or partial remission; Group B, Non responder or maternal deaths.
Data are presented as the median (range) or number (percentage) of patients and calculated by Fisher's exact test.
* $P < 0.05$ was considered statistically significant.

nonmyeloid cells on the bone marrow [20]. There was no study in the literature review to compare these prognostic factors during pregnancy.

Immunosuppressive agents and hematopoietic stem cell transplantation are the standard therapeutic method for severe AA, and could result more than 75% long-term survival rate [1,6]. For pregnancy associated AA, there were a few reported cases receiving stem cell transplantation or immunosuppressive agents in prenatal period who achieved successful maternal and fetal outcome [21,22]. Recently, supportive management by component transfusion during prenatal period for AA had reported better feto-maternal outcome [4,5]. The maternal mortality rate of pregnancy-associated AA had been reported at 20%–60% before the use of steroids and aggressive transfusion [23,24]. With the improvement of supportive treatment, the mortality rate of pregnancy-associated AA during prenatal period was less than 10% [5,6,23,24]. Among the 15 women in our series, the mortality rate was 20% (3/15). Two mothers died of sepsis within a month after delivery and 1 case died of sepsis four years after delivery due to progression of AA to MDS.

Identifying factors associated with poor maternal outcome would be helpful in patient counseling. In this study, low platelet counts, low bone marrow cellularity, and late disease presentation had a significantly difference between the uncomplicated and complicated group (Table 4). According to the present patient data and literature review, the neutrophil counts were not associated with poor maternal outcome. However, we incidentally found that late gestational age of disease occurrence resulted in poor maternal outcome. The actual cause of the relationship between the late disease presentation and complicated pregnancy was still unknown. It has been suggested that the outcome of pregnancy and maternal survival were better in women who had AA before pregnancy as compared to those developed during pregnancy [25]. Moreover, patients with pre-existing severe AA might have contraceptive because they are already aware of the risk of relapse during pregnancy, and can prepare for the risks and undergo regular blood tests and transfusions. The increased maternal morbidity and mortality at later gestation may result from rapid progression and higher risk of bleeding during later gestation.

Despite the maternal risk, the fetal outcome was good in our series. The survival rate was 100% (17/17 delivery, excluded one termination due to PPROM at 22 weeks), and have been in healthy condition for an average follow-up of five years after birth. The good prognosis of pregnancy may be related to that all the survival children had a close multidiscipline care and an optimal timing of delivery.

In conclusion, this study and literature review identified the significant factors (extremely low platelet counts, low bone marrow cellularity, and late disease presentation) affecting severe AA during pregnancy. Early recognition of such risk factors and timely management should be helpful for improving poor maternal outcomes.

Conflict of interests

All authors declared no conflict of interests.

Acknowledgements

The authors would like to thank Dr. Chao-Ning Wang M.D. PhD. for data acquisition.

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