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The Effect of Hemoglobin Correction by Blood Transfusion on Pregnancy Outcomes in Minor and Intermedia Thalassemia Patients: A Single-Blind Controlled Randomized Clinical Trial

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Abstract

To the best of our knowledge, there is no prospective trial study assessing the management of β-thalassemia by blood transfusion in pregnancy. The aim of this study was to investigate the effect of blood transfusion on maternal and neonatal outcomes in pregnant patients with beta thalassemia minor and intermedia. We did this randomized, single –blind, controlled clinical trial on 36 pregnant women with β thalassemia minor and intermedia at two tertiary hospitals of Imam Khomeini and Shafa in Ahvaz, Iran from January 2016 to July 2016. Patients were randomly assigned to receive either packed cell or not (control group) during pregnancy (ratio 1:1). The main outcomes of interest transfusion times, abortion, preterm delivery, type of delivery (cesarean or vaginal), stillbirth, birth weight, low birth weight, very low birth weight, small for gestational age, low Apgar score (≤7) at 1 and 5 minutes, oligohydramnios, fetal anomalies , and NICU admission. The median of blood transfusion in intervention group during pregnancy was two blood units. The cesarean section rate did not significantly differ between the intervention and control groups (72.2% and 44.4%, respectively, P=0.2). Two infants in intervention group experienced with LBW, one with SGA, one with low Apgar score, two with oligohydramnios, and one with NICU admission, while none in control group experienced these complications. The mean birth weight of infants in intervention group was significantly lower than control group (P value 0.002). The comparison between two groups showed that the adverse maternal and neonatal outcomes, especially low birth weight and preterm delivery were higher in intervention group.

Keywords: Beta thalassemia minor, Beta thalassemia intermedia, blood transfusion, neonatal outcomes, Apgar, low birth weight, ferritin.

1. Introduction

Thalassemia syndrome is the most common inherited blood disorders worldwide (Traisrisilp, Luewan, & Tongsong, 2009; Whiteman et al., 2013). It affects approximately 100 million people, mostly in Mediterranean, South-eastern Asia and Africa (Yordanova, Nikolov, Museva, & Karamiseva, 2013). The frequency of thalassemia in provinces around Persian Gulf, the south of Iran is high and reaches 8-10% (Zandian, Keikhaie, Pedram, Kianpoor, & Ghahfarokhi, 2009). Thalassemia is an inherited hemoglobin disorder in which mutated globin gene results in the various degrees of defects including globin production, an imbalance in alpha/beta globin chain synthesis, an ineffective erythropoiesis, and varying severity of disease and anemia (Howard, Tuck, Eissa, & Porter, 2015). In addition, it is the second reason for hypochromic anemia and anemia in pregnancy after iron deficiency (Yordanova et al., 2013).

Patients with beta-thalassemia minor and intermedia have milder clinical manifestations in compare to

beta-thalassemia major (Howard et al., 2015). The pregnancy in thalassemia major is compromised by transfusion support; however, fertility is possible in the majority of patients with thalassemia intermedia (Nassar et al., 2006). Although, beta thalassemia pregnant patients suffer from anemia with hemoglobin levels of 7-10 g/dl, also have variable degrees of splenomegaly (Nassar et al., 2006) and more likely may need to blood transfusion (Benz, 2016).

Pregnancy itself leads to various physiologic changes such as relative anemia which can put potential effects on both mother and fetus (Cunningham, Leveno, Bloom, Spong, & Dashe, 2014; Nassar et al., 2006; Rahimi, 2013; Rezaee, Banoei, Khalili, & Houshmand, 2012). Therefore, it seems that pregnancy related physiologic changes intensify underline anemia in beta thalassemia patients (both minor and intermedia) and increase the risk of preterm labor, intrauterine growth restriction, and low birth weight (Hanprasertpong et al., 2013; Nassar et al., 2006). Despite the limited number of stdies on pregnancy outcomes in patients with beta thalassemia minor and intermedia, it has been shown that the rate of some adverse complications such as IUGR and need a blood transfusion, especially in beta thalassemia intermedia, is high. This emphasizes the collaborations between hematology and obstetric services to manage such patients (Nassar et al., 2006; Voskaridou et al., 2014). Modifying the hemoglobin concentration by transfusion therapy is one of the most effective procedures to improve hematologic and tissue oxygenation status (S. Sharma, P. Sharma, & Tyler, 2011; Voskaridou et al., 2014). On the other hand, blood transfusion has its inherited complications, i.e. immunologic hemolytic anemia, so that the decision on time of transfusion is always challenging (Dzik et al., 2011). There is no evidence on the minimum hemoglobin level in pregnant women with beta thalassemia, and hemoglobin level modifications are performed on the basis of data from retrospective studies (Voskaridou et al., 2014).

It is logical that the decision on blood transfusion necessity is conducted to reach to the hemoglobin levels with least complications on pregnancy outcomes, to provide appropriate conditions for fetal growth and to decrease unnecessary blood transfusion. Currently, there is no consensus and also clinical trial on goal hemoglobin level in pregnant patients with beta thalassemia minor and intermedia. Hence, the aim of this randomized, single-blind, controlled clinical trial was to investigate the effects of blood transfusion on maternal and neonatal outcomes in pregnant patients with beta thalassemia minor and intermedia.

2. Materials and Methods

We did a This is a randomized, single-blind, controlled clinical trial which conducted on 36 pregnant women with β thalassemia minor and intermedia at two tertiary hospitals of Imam Khomeini and Shafa in Ahvaz, Iran from January 2016 to July 2016. The study was approved by ethical committee of Ahvaz Jundishapur University of Medical Sciences (Ethics code: IR.AJUMS.REC.1394.562). Also the study was registered at www.irct.ir and received a clinical trial registration number of IRCT2016010825903N1.

Inclusion Criterion for both intervention and control group was hemoglobin level at range of $7 \leq Hb \leq 8.5$ g/dl during first trimester of pregnancy and thalassemia was diagnosed based on hemoglobin typing. The exclusion criteria were twin pregnancy, chronic diseases such as rheumatology and antiphospholipid autoimmune syndrome, known genetic disorders, the age above 35 years, and metabolic diseases such as cushing's syndrome, hyperthyroidism, hypothyroidism, and hypoadrenalism.

Patients were randomly assigned into two groups to receive either pack cell or not (control group) during pregnancy. Accordingly, 18 pregnant women with β thalassemia as intervention group received pack cell during their pregnancy period and 18 pregnant women with β thalassemia as control group did not receive pack cell. All patients according to hematologist prescription were treated with acid folic (5 mg/day) and ferrosulfat (based on serum ferritin levels). In addition all participants received routine prenatal care and also Hb variations were evaluated. During prenatal care, the fetal health status was monitored using biometry ultrasonographic procedure at 30 and 34 weeks of gestation. Moreover, color Doppler of umbilical artery was performed if necessary.

The main outcomes of interest were transfusion times (number of packed cell units), abortion, preterm delivery (<37 gestational weeks), type of delivery (cesarean or vaginal), stillbirth (death in utero after week 24 of gestation), low birth weight (LBW<2500 gr), very low birth weight (VLBW<1500 gr), small for gestational age (SGA: birth weight< 10^{th} percentile for gestational age), , oligohydramnios, low Apgar score (≤7) at 1 and 5 minutes, fetal anomalies, and NICU admission. Laboratory tests included hemogram analysis (Hb, MCV, MCH, SGOT, SGPT, ferritin, and total bilirubin).

The data was analyzed using the SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The mean±standard deviation and frequency (percentage) were used for summarizing of quantitative and qualitative variables, respectively. Non-parametric Mann-Whitney U Test was

utilized to compare the mean values of hemoglobin, ferritin, SGOT, SGPT, bilirubin, MCH and MCV between two groups. In addition, Chi square test was used to compare proportions between categorical and nominal variables. The P value levels less than 0.05 was deemed as statistically significance.

3. Results

In total, 36 singleton pregnant women with β-thalassemia minor and intermedia were analyzed, 18 patients in intervention group and 18 patients in control group to receive blood units and 18 without receiving blood units as control group. The demographic and history characteristics are reviewed in Table 1. The mean age score of women in intervention group (27.5 ± 5.2 years) did not differ significantly from this in control group (30.5 ± 2.5) (P value= 0.17). Patients in control group mostly (16 subjects of 18) did not have the history of abortion, while in intervention group 8 patients (44.4%) had no history of abortion, 6 patients (33.3%) had one previous abortion, 2 patients (11.1%) had two previous abortion, and 2 patients (11.1%) had three or higher abortion rate, although the history of abortion did not differ significantly between two groups (P value = 0.063). Similarly, two groups were matched in terms of gravida and parity (P value = 0.8 and 0.4, respectively) (Table 1).

Table 1. Demographic and history characteristics of pregnant women with β thalassemia

Variables		Transfusion		P value
		Intervention group (n=18)	Control group (n=18)	
Age (yr)		27.5 ± 5.2	30.5±6.5	0.17
Number of Abortions	0	8 (44.4%)	16 (88.8%)	0.063
	1	6 (33.3%)	1 (7.1%)	
	2	2 (11.1%)	1 (7.1%)	
	3	2 (11.1%)	0	
Gravida	1	7 (38.8%)	4 (22.2%)	0.8
	2	6 (33.3%)	6 (33.3%)	
	3	2 (11.1%)	4 (22.2%)	
	>=4	2 (11.1%)	4 (22.2%)	
Parity	0	8 (44.4%)	3 (21.4%)	0.4
	1	4 (22.2%)	4 (28.6%)	
	2	3 (16.6%)	3 (21.4%)	
	>=3	3 (16.6%)	4 28.6%)	

Significance level: less than 0.05.

The mean Hb score in intervention group (7.8 ± 0.9) at baseline was significantly lower than mean Hb score in control group (8.2 ± 0.4) at baseline (P value = 0.05). However, the mean Hb level score had borderline significance difference between two groups. In addition this difference was statistically significance not clinically. There was significant difference in mean MCV between intervention and control groups (65.9 ± 4.4 μm^3 and 61.1 ± 5.7 μm^3) (P value = 0.02). SGOT, SGPT and total bilirubin scores were matched between two groups (Table 2).

Table 2. Baseline laboratory tests of pregnant women with β thalassemia

Variable	Transfusion		P value
	Intervention group (n=18)	Control group (n=18)	
Hemoglobin (gr/dL)	7.8 ± 0.9	8.2 ± 0.4	0.05
MCH (pg)	18.3 ± 1.8	20.8 ± 1.9	0.007
MCV (μm^3)	59.8 ± 4.2	65.9 ± 4.4	0.002
SGOT (IU/L)	22.3± 4.4	20.2± 2.1	0.4
SGPT (IU/L)	25.9 ± 4.2	23.3 ± 1.1	0.2
Total bilirubin (mg/dL)	0.8 ± 0.2	0.9 ± 0.3	0.3

Significance level: less than 0.05.

The profile of received packed cell is depicted in Figure 1. Overall, in intervention group during entire pregnancy, 10 patients (55.5%), 7 patients (38.8%) and only one patient (5.5%) received one, two and three blood units, respectively.

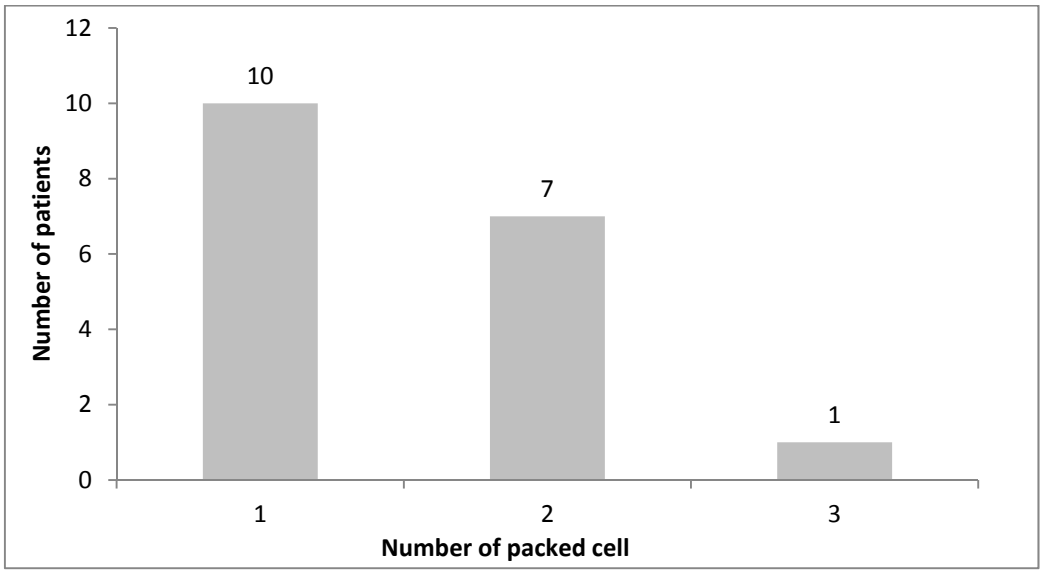

Figure 1. Nuumber of received packed cell in intervention group

The maternal and neonatal outcomes in pregnant women with β thalassemia are represented in Table 3 and Table 4. In total, two patients underwent induced abortion, one in intervention group due to hydrops fetalis and one case in control group due to fetus with thalassemia major. Cesarean section was performed in 13 patients (72.2%) in intervention arm and in 10 patients (55.5 %) in control arm. There was no significant difference in cesarean section rate (P value= 0.2). The reasons for undergoing cesarean section in 13 cases of intervention group were as follows: 3 cases with previous cesarean section, two cases for the mother's request and 8 cases due to precautionary reasons. Three cases experienced fetal anomaly, one case was in intervention arm and two cases were in control arm. None of study patients reported splenomegaly.

The mean birth weight score for patients in intervention group (2816.2 ± 525.6 gr) was significantly lower than control group (3463.1 ± 628.8 gr) (P value = 0.002). The number patients with preterm delivery in intervention group (5 cases) was higher than this control group (no case), although the rate of preterm delivery did not differ significantly between two groups (P value = 0.07). None of patients in both intervention and control group reported stillbirth. Three cases with low Apgar score at 1 and 5 minutes (≤7) were reported in intervention arm. Two patients had oligohydramnios fetuses which all were in intervention arm and none were in control arm (P value=0.12). Of 18 cases in intervention group, one neonate needed NICU hospitalization. There was no event of NICU hospitalization in control group.

Table 3. Maternal outcomes of pregnant women with β thalassemia

Variable		Transfusion		P value
		Intervention group (n=18)	Control group (n=18)	
Abortion	Yes	1 (5.5%)	1 (5.6%)	0.6
	No	17 (94.4%)	17 (94.4%)	
Type of Delivery	Vaginal	5 (27.7%)	8 (44.4%)	0.2
	Cesarean	13 (72.2%)	10 (55.5%)	
Reasons of cesarean delivery	Previous cesarean section	3	8	
	Mother's request	2	2	
	Precautionary reasons	8	0	
Preterm delivery	Yes	3 (16.6%)	0	0.07
	No	15 (83.3%)	18 (100%)	

Significance level: less than 0.05.

Table 4. Neonatal outcomes of pregnant women with β thalassemia

Variable		Transfusion		P value
		Intervention group (n=18)	Control group (n=18)	
Fetal anomaly	Yes	1 (5.5%)	2 (11.1%)	0.5
	No	17 (94.4%)	16 (88.9%)	
Birth weight		2852.5 ± 428.5	3463.1 ± 628.8	0.002
Birth weight in women with term delivery		2911.9 ± 459	3463.1 ± 628.8	0.015
Birth weight categories	VLBW	0	0	
	LBW	2	0	
	SGA	1	0	
Low Apgar score at 1 and 5 minutes (≤7)	Yes	1 (5.5%	0	0.2
	No	17 (94.4%)	18	
Stillbirth	Yes	0	0	0.07
	No	18 (100%)	18 (100%)	
Oligohydramnios	Yes	2 (11.1%)	0 (11.1%)	0.12
	No	16 (88.8%)	18 (88.9%)	
NICU admission	Yes	1 (5.5%)	0	0.2
	No	17 (94.4%)	18 (100%)	

Significance level: less than 0.05.

The serum ferritin concentrations in different groups are summarized in Table 5. Patients in intervention group developed significantly higher ferritin level (80.7 ± 68.2 µg/mL) than control group (44.3 ± 27.4 µg/mL) (P value<0.0001). The inverse association was observed between serum ferritin level and birth weight (r= -0.6, P value= 0.026).

Table 5. Comparing of serum ferritin levels between two groups

Variable	Intervention group	Control group	P value
Ferritin (µg/mL) (in total patients)	80.7 ± 68.2	44.3 ± 27.4	<0.0001
Ferritin (µg/mL) (in term pregnancies)	99.3±83.1	44.3±27.4	<0.0001

Significance level: less than 0.05.

4. Discussion

To the bets of our knowledge, there is no clinical trial has investigated the effect of hemoglobin level modification with transfusion on pregnancy outcomes both on neonatal and maternal outcomes in pregnant women with beta thalassemia intermedia. Our search showed that all researches on this issue are limited to retrospective studies. Current clinical trial assessed the effect of hemoglobin level modification using transfusion on pregnancy outcomes including birth weight, preterm deliveries, abortion, cesarean section, low Apgar score (≤7), fetal anomaly, oligohydramnios and NICU admission in pregnancies with beta thalassemia intermdedia and minor.

Low Hb levels in early pregnancy may lead to adverse neonatal outcomes (Traisrisilp et al., 2009). The effect of blood transfusion on pregnancy outcome has potential importance (Howard et al., 2015). Pregnant women with beta thalassemia intermedia who infrequently receive blood transfusion expose to the risk of alloimmunization. Therefore, the risk of low birth weight and preterm delivery should be balanced with the risk of alloimmunization (Howard et al., 2015). Currently Transfusion therapy is not routine treatment of beta thalassemia intermedia. The decision on regular blood transfusion is difficult due to heterogeneity of the disease. There are evidence in which anemia (100 g/l) is an independent risk factor for low birth weight and preterm delivery in non-thalassemic pregnant women (Levy, Fraser, Katz, Mazor, & Sheiner, 2005). Chronic anemia in pregnant women may result in fetal hypoxia and lead to IUGR (Nassar et al., 2006). Eyal Sheiner et al., in their study could not find significant relationship between hemoglobin level and IUGR incidence in women with thalassemia. It has been shown that the different mechanism other than hemoglobin level is responsible for IUGR in women with thalassemia minor (Sheiner, Levy, Yerushalmi, & Katz, 2004). At least, one study has found spleen infarction in patients with thalassemia minor (Liaw, Kotkiewicz, & Kender, 2009). This mechanism leads to placenta insufficiency; however, this theory needs more investigation to be approved. In another study, it has been shown that all adhesion molecules and CRP (C-reactive protein) increase in patients with thalassemia intermedia (Kanavaki et al., 2009). Hence, inflammation and such molecules may cause placenta infarction in patients with thalassemia minor (Amooee, Samsami, Jahanbakhsh, & Karimi, 2011). In the present study, patients in intervention group mostly received one or two blood units (median of 2 units) during pregnancy to maintain the hemoglobin level over 7 g/dl. In our study, the inclusion criterion for both groups was Hb level between 7-8.5 g/dl, however, at analysis we found borderline significance difference in terms of mean Hb level between two groups which had not conflict with our inclusion criteria. Despite two groups were matched in terms of Hb concentration, nevertheless, we observed two infants with LBW (birth weight < 2500 g) (11.1%), one case of SGA (5.55%) and 3 preterm delivery (14.4%) in intervention group. There was no case of LBW, SGA or preterm pregnancy in the control group. Several retrospective studies on pregnant women with beta thalassemia who received blood transfusion during pregnancy to maintain Hb levels above 7 g/dl have reported the high incidence of SGA, LBW and preterm delivery. In a retrospective study by Traisrislip et al., this was conducted on 77 pregnancies with thalassemia intermedia to maintain Hb levels above 7 g/dl by blood transfusion with the mean transfusion of 1.4 units. They have reported the rates of 44.1%, 3.27%, 20.8% and 32.5% for LBW, SGA, preterm delivery and cesarean section, respectively. The mean birth weight in their study is 2572±501 gr (Traisrisilp et al., 2009). Another study (Luewan, Srisupundit, & Tongsong, 2009) has retrospectively assessed 54 women with beta thalassemia intermedia. The mean blood transfusion is 2.4 packed cells (range: 1-5 units) to keep Hb levels above 7 g/dl. They have observed that the rates of IUGR, preterm pregnancy, and low birth weight are 44.4%, 35.2% and 70.4%, respectively. Moreover, Nassar et al., in a study have showed that IUGR complicating 24.4% of pregnancies with beta thalassemia intermedia (Nassar et al., 2008). The range of blood transfusion in women with Hb levels of 7.6 g/dl varies from 1 unit for whole pregnancy to 1 unit per week and the mean birth weight is 3075 ± 490 gr in a study from Italy (Origa et al., 2010). In present study, the mean birth weight of term pregnancies in intervention group (2961.1 ± 454.8 g) was slightly lower than the mean birth weight that has been reported by Origa et al. We observed that the rate of delivery by cesarean section was high involving 72.2% and 55.5% of relevant pregnancies in intervention and control groups, respectively.

Table 6. Comparison between outcomes of interest in the literature in beta thalassemia pregnant women who

received blood transfusion

Author		Sample size	Type of study	Birth weight (grams)	LBW	SGA	Preterm delivery	Cesarean section	Transfusion regimen (range or mean)
Nassar et al., 2008		83	Retrospective	2551±621	NR	24.4%	31.8%	72.2%	NR
Traisrislip et al., 2009		77	Retrospective	2527.14± 251	44.1%	3.27%	20.8%	32.5%	1.4
Luewan et al., 2009		54	Retrospective	NR	70.4%	44.4%	35.2%	27.8%	2.4
Origa et al., 2010		17	Retrospective	3075±490	NR	NR	11.8%	27.7%	1 per whole pregnancy-1 per week
Current study	Intervention	18	Clinical trial, Prospective	2852.5±28.5	2 (11.5%)	1(5.55%)	3(14.4%)	72.2%	1-3
	Control	18		3463.1±628.8	0	0	0	55.5%	0

NG: not reported.

The rate of cesarean section has been reported in various retrospective studies conducted on pregnant women with beta thalassemia who have received blood transfusion. These rates in various studies were 72.2%, 27.7% and 32.5% (Nassar et al., 2008; Origa et al., 2010; Traisrisilp et al., 2009). The comparison between outcomes of interest in the literature is shown in Table 6. Voskaridou et al., have also reported that the cesarean section accounted for half of pregnancies with beta thalassemia intermedia mainly for suboptimal fetal growth. Their study population was transferred when Hb levels are lower than 8 g/dl (Voskaridou et al., 2014).

We found that the mean serum ferritin level at third trimester in intervention group was about two fold higher than this in control group (Table 5). In addition, preterm pregnancies of our study in intervention group had higher serum ferritin level compared with the control group (Table 5). Two previous studies have shown that there is association between serum ferritin level and preterm delivery (Amooee et al., 2011; Scholl, 1998). We observed that pregnancies with SGA had significantly higher serum ferritin level compared to pregnancies with LBW or normal birth weight. This well confirmed by a number of retrospective studies which have also demonstrated that the increase in serum ferritin level is associated with the higher risk of SGA in pregnancies with beta thalassemia intermedia (Gaspar, Ortega, & Moreiras, 1993; Origa et al., 2010; Uberos, 2000; Višnjevac, Segedi, Ćurčić, Višnjevac, & Stajić, 2011). Pregnancies complicated by IUGR have higher serum ferritin level due to decrease in ferritin and iron absorption by placenta (Bashiri, Burstein, Sheiner, & Mazor, 2003; Cogswell, Parvanta, Ickes, Yip, & Brittenham, 2003; Ćujić D, 2011; Haram, Svendsen, & Myking, 2007; Ronnenberg et al., 2004; Uberos, 2000).

Other complications which had been observed in our study in intervention group included 1 case of stillbirth, 1 case with low Apgar score (<=7), two cases of fetal anomaly, two cases of oligohydramnios, and 1 case need NICU admission. In the control group, except two cases of fetal anomalies no other complication was reported.

Finally, the incidence of adverse pregnancy outcomes was lower than previously retrospectively conducted studies. Probable explanation for the lower rate of complications in the present study may be related to prospectively and exact monitoring of both intervention and control groups. Another explanation is the study population heterogeneity (beta thalassemia minor and intermedia).

The strength of this follow-up study is that the data were collected as part of a prospective, randomized controlled trial. The limitation of the study was the heterogeneity (beta thalassemia minor and intermedia) of the study patients. Another limitation is small sample size.

The comparison between transfused pregnant women with beta thalassemia minor and intermedia with Hb level of 7-8.5 g/dl and those without transfusion with the same Hb level showed that the adverse pregnancy outcomes, especially low birth weight and preterm delivery were higher in transfused patients. In addition, the mean serum ferritin level had significant relationship with transfusion and birth weight.

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Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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