Pregnancy and childbirth in women with thalassemia: past and present

This is a multicenter retrospective study (26 Italian centers) supported by the Italian Society of Thalassemia and Hemoglobinopathies (SITE) to assess how the advances of the last decades have affected pregnancy outcomes in transfusion-dependent β thalassemia (β-TDT) women (N=251, 346 pregnancies) and their newborns during the period 1992-2024 (*Online Supplementary Table S1*). The study was approved by the Ethics Committee of the participating centers, registered with clinicalTrials.gov (*clinicaltrials gov. Identifier: NCT06889727*; Observational Studies Register - AIFA: 1817), and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients.

Two patients (0.8%) had four pregnancies, 16 of 251 (6.4%) had three, 57 of 251 (22.7%) had two, and 176 of 251 (70.1%) had one; 291 pregnancies resulted in live babies, eight of 346 (2.3%) were ongoing, 22 of 346 (6.4%) ended in spontaneous abortion, seven of 346 (2.0%) were voluntarily terminated (Figure 1A). In three cases (0.9%), intrauterine fetal death occurred, accounting for four deaths. Maternal age at first pregnancy increased significantly over time (β=0.19, 95% confidence interval [CI]: 0.09-0.28; *P*<0.001), similar to non-thalassemic Italian women.[1] Ovulation was spontaneous in 178 of 314 (56.7%) pregnancies, whereas gonadotropins were administered in 136 of 314 (43.3%). *In vitro* fertilization (IVF) was performed in 54 pregnancies, including 52 after gonadotropin-induced ovulation and two after spontaneous ovulation (Figure 1B). Ovarian donation was employed for IVF in 12 patients.

Older patients were less likely to achieve spontaneous conception (odds ratio [OR]=0.81; 95% CI: 0.75-0.87; *P*<0.001), whereas it has become more likely in recent years than in earlier periods (OR=1.08; 95% CI: 1.03-1.14; *P*=0.004). This aligns with other studies showing that the likelihood of hypogonadism diminishes over time and that a decreasing percentage of patients do not spontaneously reach menarche. Preimplantation diagnosis was performed in 11 of 306 cases (3.6%). Among the 294 completed pregnancies, 37 were twin pregnancies, including one with a stillborn twin. Three pregnancies involved triplets, with one case of first-trimester embryo reabsorption. An association was found between twin pregnancies and the year of conception (OR=0.94; 95% CI: 0.89-0.99; *P*=0.018), ovulation type (gonadotropin-induced *vs*. spontaneous; OR=6.48; 95% CI: 2.87-16.6; *P*<0.001) and conception type (non-spontaneous *vs*. spontaneous; OR=2.94; 95% CI: 1.40-6.20; *P*=0.004). With multivariate analysis only the type of ovulation remained statistically significant (OR=5.23; 95% CI: 1.87-15.7; *P*=0.002). Three newborns were β-TDT homozygotes. Complications during pregnancy were reported in 124 of 252 (49%) pregnancies (Figure 2). Due to the retrospective design, some miscarriages may have gone unreported. Nonetheless, to our knowledge, the frequency of miscarriages and threatened miscarriages was similar to that in non-thalassemic women.[2,3] Gestational diabetes[4] (28 patients, 16.9%) and renal colic[5] (11 patients, 6.6%) were the only complications that were more frequent when compared to the general population. In contrast, our study did not support an increased incidence of pre-eclampsia (25, 15.1%), which has already been highlighted in other studies.[20,21] Notably, we found that the likelihood of pre-eclampsia decreased significantly over time (OR=0.93; 95% CI: 0.87-0.99; *P*=0.017). Multivariate logistic analysis confirmed that complications were likely to occur in older patients (OR=1.09; 95% CI: 1.02-1.17; *P*=0.016) and those with pre-existing comorbidities (OR=1.33; 95% CI: 1.11-1.62; *P*=0.003).

Thrombotic events occurred during pregnancy in three women and the peripartum period in one: two were splenectomized. Forty-four women were already on antiplatelet therapy when they became pregnant, whereas three were on anticoagulant therapy. Fifty-eight women commenced antithrombotic therapy during pregnancy (median week 6.5, Q1-Q3: 2-20; 18 acetylsalicylic acid, 35 low-molecular-weight heparin, 4 both, and 1 ticlopidine), highlighting the lack of definitive evidence and universally accepted recommendations and guidelines. Like other studies, our analysis confirms that serum ferritin and liver iron concentration (LIC) increase, because of non-chelation and increased transfusion requirements (Table 1; *Online Supplementary Figure S3*). Our experience on cardiac-T2* during pregnancy is the largest hitherto published. In our cohort, most women started gestation without cardiac iron load, which persisted until the end of pregnancy. However, where occurred, it was not possible to correlate cardiac iron during pregnancy with basal LIC or transfusions, suggesting other factors, including genetic predisposition to organ-specific iron load. Numerous other factors affect cardiac function during pregnancy (increased blood volume, pressure changes, increased heart rate and cardiac output, and interruption of chelation).[8] While on average we confirmed that cardiac function was not impaired during pregnancy, three women presented cardiac symptoms during or soon after pregnancy, with one experiencing iron-related heart failure and bilateral ovarian vein thrombosis during delivery. In pregnancies achieved with ovarian stimulation, the number of women with iron overload at baseline (cardiac-T2* <20 ms and/or LIC >7 mg/g dry weight) decreased over time (OR=0.85; 95% CI: 0.70-0.99; *P*=0.055), with no pregnancies showing iron overload after 2016. This may reflect adherence to Good Clinical Practices regarding pregnancy in TDT, though it could

also be due to fewer patients with significant iron overload.[9] Notably, in pregnancies with documented severe hemosiderosis, considering the risk/benefit ratio, resuming chelation with desferrioxamine (DFO) in the last trimester is possible and appropriate, as reported in our study in eight patients, two of whom had taken cardiologic drugs for previous left ventricular ejection fraction (LVEF) reduction. Conversely, in some centers in Italy, very low doses of DFO are offered to all pregnant women with TDT, even having started the pregnancy with optimal iron status, to limit the circulating free iron, which is toxic. This approach may positively affect the condition of the heart, which is subject to considerable stress during pregnancy as a result of the aforementioned factors. No significant differences (*P*=0.62) were observed between the pre- and post-pregnancy LVEF values (median difference 0%, Q1-Q3, -1.5 to 1). However, 12 women started pregnancy with LVEF <56% and two of them had cardiac overload at baseline. Fifteen had abnormal values during pregnancy, six of whom had LVEF<56% at baseline.

Of all deliveries, only 20 (6.8%) were vaginal, 225 (77.1%) were planned cesarean sections, predominantly for precautionary reasons (89/225), and 45 (15.4%) were emergency cesarean

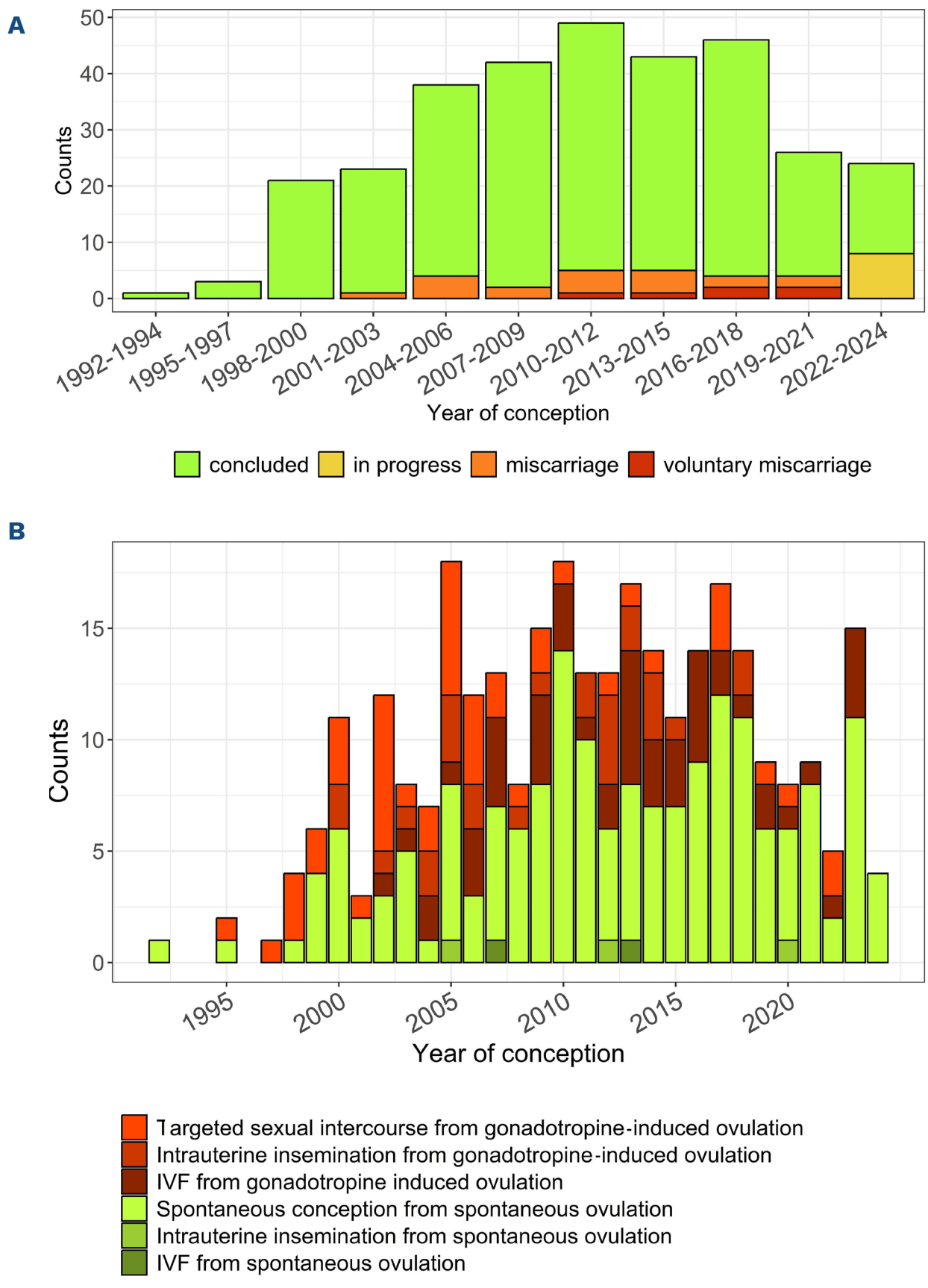

Figure 1. Pregnancies in transfusion-dependent Thalassemia patients. (A) Number of pregnancies in function of the year of conception and outcome. (B) Type of conception in function of the year of conception. IVF: *in vitro* fertilization.

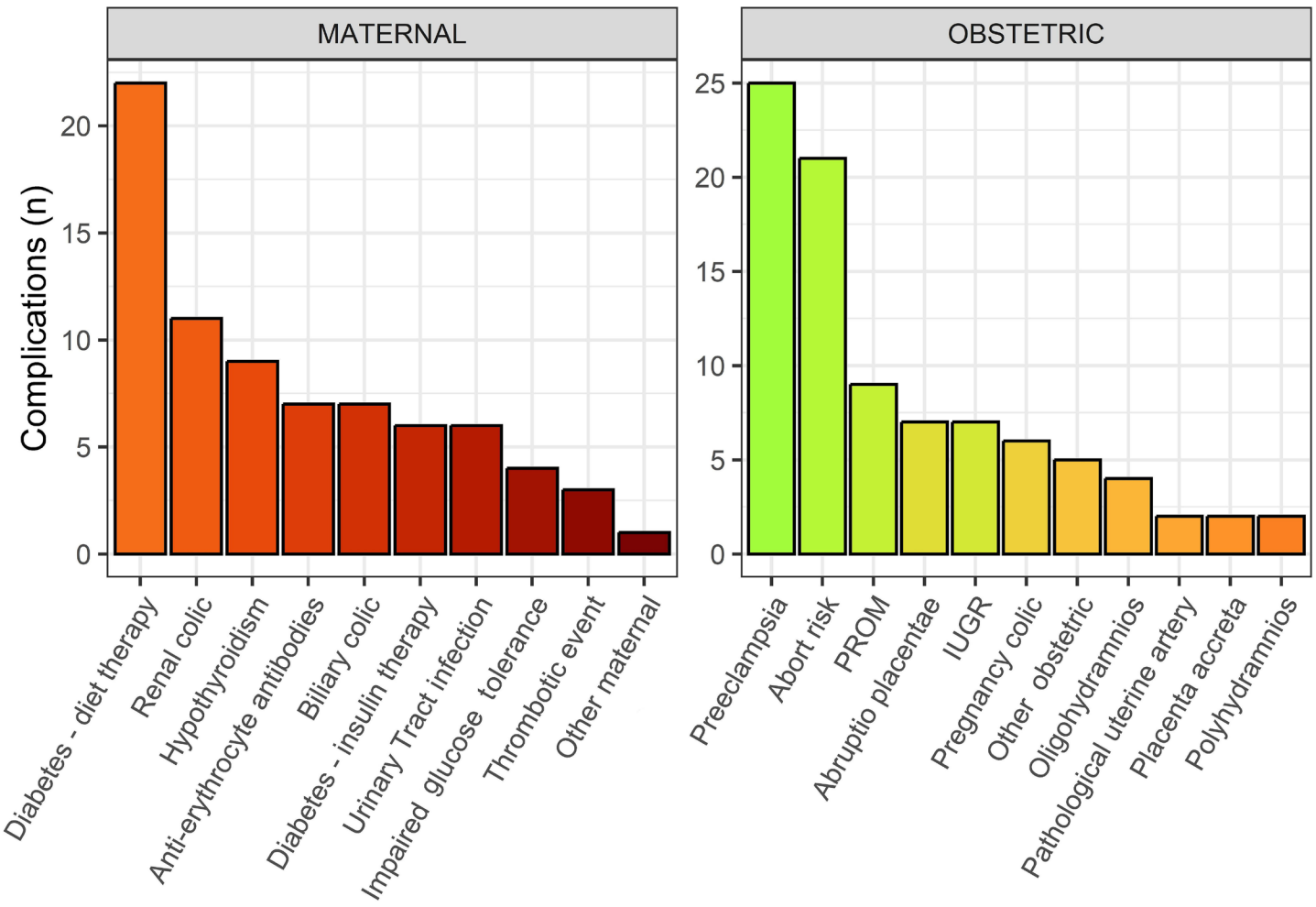

Figure 2. Complications during pregnancy. Number of complications during pregnancy ordered by frequency (in the category "Other obstetric": chorioamnionitis [1], early onset of labor [1], hydronephrosis [1], reabsorption of a fetus [1], threat of premature birth [1]; in the category "Other maternal": H1N1 infection [1]). PROM: premature rupture of membranes; IUGR: intrauterine growth restriction.

sections. The number of cesarean sections did not decrease over time (*P*=0.7) nor was it associated with maternal age (*P*=0.2). Although TDT is no longer considered an absolute indication for cesarean delivery, it continues to be routinely recommended by most gynecologists, significantly more than those described worldwide, even in Italy, which has one of the highest rates of cesarean sections in the world.[10-11]

Overall, 16 women experienced postpartum complications (*Online Supplementary Table S2*).

Preterm births were 111 of 284 (38.8%). The percentage of preterm births significantly declined over time (β=–1.4; 95% CI: -2.5 to -0.24; *P*=0.02), decreasing from 49.2% in 2003 to 21.6% in 2023. The high incidence of twin pregnancies may be a contributing factor in this respect. The frequency of babies requiring admission to the neonatal intensive care unit (74 newborns, 56 preterm) was nonetheless higher than in the general population.[12]

The median birth weight was 2,770 g (Q1-Q3: 2,232-3,047 g). An increase in birth weight was observed over time (β=23 g/year; 95% CI: 9-38; *P*=0.002), with an increase of about 500 g from 2003 to 2023. The reduction of preterm deliveries and of the number of twin pregnancies contributed significantly to the increase of birth weight. Newborn weight appropriateness was assessed in 133 pregnancies with available gestational age data: 107 (80.5%) were appropriate for gestational age, seven (5.3%) were large, and 19 (14.3%) were small (SGA). SGA infants included seven from single pregnancies and six from multiple pregnancies. No correlation was found between ferritin level and/or LIC and the risk of preterm birth or SGA. The number of SGA babies did not decrease over time (*P*=0.8). Nevertheless, the improvement in neonatal outcomes can reasonably be attributed to advances in conventional therapy.[13] Neonatal complications, excluding malformations, were reported in 36 pregnancies (*Online Supplementary Table S2*). The rate of newborns with malformations matched the general population. In the seven cases of malformations, no association was found with late withdrawal of chelation therapy after conception. Two women received two doses of luspatercept (1 mg/kg, administered 3 weeks apart) without complication.[14]

In 49 of 225 (21.8%) pregnancies, iron chelation therapy was stopped at the time of conception, whereas in 176 of 225 (78.2%), it was discontinued later, with a median delay of 4 weeks after conception (Q1-Q3, 3-6). No significant difference between chelators was found (*P*=0.11). In 13 women, iron chelation therapy was continued for ≥12 weeks post-conception without adverse consequences.

A subset of eight patients resumed iron chelation therapy during pregnancy after a median of 20 weeks (Q1-Q3, 18.2-24.5); only two of which had a history of LVEF reduction.

According to institutional data, 57% of children born in

Table 1. Iron overload and transfusion burden.

	Baseline, median (Q1-Q3)	Follow-up,* median (Q1-Q3)	Variation,# median (Q1-Q3)	N	*P*§
Pre-transfusion Hb, g/dL	9.5 (9.3-9.9)	9.8 (9.5-10.2)	0.29 (0.20-0.35)	185	<0.001
Post-transfusion Hb, g/dL	12 (11-12.5)	12.4 (11.4-12.5)	0.20 (0.10-0.35)	117	0.0038
Blood consumption, mL/kg/year	145 (123-175)	150 (115-200)	9.9 (3.8-16)	140	0.007
Ferritin, ng/mL	900 (503-1,400)	1,900 (1,300-2,894)	973 (844-1,106)	209	<0.001
Cardiac-T2*, ms	33.2 (26.1-40.2)	33 (23.9-39)	-1.1(-3.2 to 0.9)	99	0.21
LIC, m/g d.w.	2.5 (1.7-5.3)	8.4 (4.8-12.3)	5.1 (4.1-6.1)	101	<0.001

Follow-up evaluated during pregnancy; for ferritin, liver iron concentration (LIC) and cardiac-T2 follow-up evaluated after pregnancy. #Median variation estimated with Hodges-Lehmann estimator. §Wilcoxon signed-rank test for paired samples or paired *t* test. Hb: hemoglobin, Q1-Q3: interquartile range (25th-75th percentile); ms: milliseconds; LIC: liver iron concentration; d.w.: dry weight.

Italy are exclusively breastfed for 3 months, whereas the percentage in our cohort was lower.[15] Exclusive or mixed breastfeeding was chosen for 118 children, with a median duration of 2 months (Q1-Q3, 1-5). Although an increasing trend in breastfeeding over time was observed, it was not statistically significant (*P*=0.2).

In TDT women, many aspects of pregnancy and neonatal outcomes have improved with better disease management. Nevertheless, whether spontaneous or planned, pregnancy in TDT should only occur when the woman is in optimal health and in the absence of significant comorbidities. This is due to the potential risks associated with introducing new, potentially teratogenic medications, and to the worsening of iron accumulation, particularly in the heart. The increasing preservation of fertility and spontaneous conception add further complexity and highlight the importance of counseling to reinforce information and prevent unplanned pregnancies. It also calls for further investigation into the safety/efficacy of reintroducing iron chelation after the first trimester of pregnancy, regardless of pre-pregnancy iron status.

Additionally, significant uncertainties persist, including the thrombotic risks associated with pregnancy. Determining who is at risk and identifying the most effective preventive strategies remain critical areas for further investigation.

Authors

Anna Demurtas,[1*] Barbara Gianesin,[2*] Antonietta Zappu,[3] Elena Cassinerio,[4] Simona Leoni,[4,5] Paolo Ricchi,[6] Carmina Fatigati,[6] Giovan Battista Ruffo,[7] Francesca Miciotto,[7] Domenico Roberti,[8] Immacolata Tartaglione,[8] Anna Maria Pasanisi,[9] Filomena Longo,[10] Francesco Sorrentino,[11] Alessandra Salvo,[12] Lucia De Franceschi,[13,14] Roberto Lisi,[15] Mauro Murgia,[16] Valentina Pisano,[17] Paola Maria Grazia Sanna,[18] Epifania Rita Testa,[19] Isabella Atzeni,[20] Raffaella Mariani,[21] Caterina Giovanna Valentini,[22] Francesco Arcioni,[23] Luca Barcella,[24] Martina Culcasi,[10] Angelantonio Vitucci,[25] Eleonora Miulli,[26] Pellegrina Pugliese,[27] Ilaria Fotzi,[28] Cristina Paci,[29] Susanna Barella,[3] Antonia Gigante,[2] Gian Luca Forni[2,30] and Raffaella Origa[1,3]

[1]Università degli studi di Cagliari, Dipartimento di Scienze Mediche e Sanità Pubblica, Cagliari; [2]FORANEMIA ETS Foundation, Genoa; [3]S.C. Centro delle Microcitemie e Anemie Rare, ASL Cagliari, Cagliari; [4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SC Medicina ad Indirizzo Metabolico, Milan; [5]Dipartimento di Scienze Cliniche e di Comunità, Dipartimento di Eccellenza 2023-2027, University of Milan, Milan; [6]Unità Operativa Semplice Dipartimentale Malattie Rare del Globulo Rosso, Azienda Ospedaliera di Rilievo Nazionale "A. Cardarelli", Napoli; [7]U.O. Ematologia con Talassemia, ARNAS Civico Di Cristina Benfratelli, Palermo; [8]Dipartimento della Donna, del Bambino e di Chirurgia Generale e Specialistica, Università degli Studi della Campania "Luigi Vanvitelli", Napoli; [9]Centro della Microcitemia A.Quarta, Hematology Unit, A. Perrino Hospital, Brindisi; [10]Day Hospital della Talassemia e delle Emoglobinopatie, Azienda Ospedaliero Universitaria S. Anna, Ferrara; [11]U.O. Talassemici Centro Anemia Rare e Disturbi del metabolismo del Ferro ASL ROMA 2 Ospedale S Eugenio, Roma; [12]U.O.D. of Talassemia, Umberto Primo Hospital, Siracusa; [13]Department of Engineering for Innovative Medicine, University of Verona, Verona; [14]Azienda Ospedaliera Universitaria di Verona, Verona; [15]Thalassemia Unit, ARNAS Garibaldi, Catania; [16]Department of Life Sciences, University of Trieste, Trieste; [17]U.O. Medicina Trasfusionale Carbonia-Iglesias, Carbonia-Iglesias; [18]Servizio Trasfusionale Aziendale, Azienda Ospedaliero-Universitaria di Sassari, Sassari; [19]Blood Transfusion Department, Santa Maria degli Angeli Hospital, Pordenone; [20]Centro Trasfusionale P.O. NS di Bonaria - San Gavino M.le (ASL Medio Campidano), San Gavino Monreale; [21]SSD Malattie Rare, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Gerardo dei Tintori, Monza; [22]Fondazione Policlinico Universitario A. Gemelli IRCCS-Roma, Roma; [23]Pediatric Oncology-Hematology Unit, Santa Maria della Misericordia Hospital, Perugia; [24]Department of Immunohematology and Transfusion Medicine, Hospital "Papa Giovanni XXIII", Bergamo; [25]Hematology and Bone Marrow Transplantation Unit, AOUC Policlinico, Bari; [26]U.O.C. Immunoematologia e Medicina Trasfusionale - Azienda USL Toscana Sud Est - PO San Donato, Arezzo; [27]Azienda Ospedaliero-

Universitaria Policlinico Umberto I Roma, Roma; [28]Centro di Eccellenza di Oncologia ed Ematologia Pediatrica - Azienda Ospedaliera, Universitaria Meyer IRCCS, Firenze; [29]U.O.S.D. Immunoematologia e Medicina Trasfusionale - Azienda USL Toscana Sud Est - P.O., Santa Maria alla Gruccia and [30]Hematology Unit IRCCS Giannina Gaslini, Genoa, Italy

*AD and BG contributed equally as first authors.

Correspondence:
R. ORIGA - raffaella.origa@unica.it

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Disclosures

No conflicts of interest to disclose.

Contributions

RO, BG and AD made substantial contributions to the conception and design of the study and performed data analysis and interpretation. AD, AZ, EC, SL, PR, CF, GBR, FM, DR, IT, AMP, FL, FS, AS, LDF, RL, MM, VP, PMGS, ERT, IA, RM, CGV, FA, LB, MC, AV, EM, PP, IF, CP and RO acquired data. GLF and SB contributed to the data analysis and interpretation. AG and AZ provided administrative support. All authors discussed the results and contributed to the final manuscript.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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