The prevalence and outcomes of \(\alpha-\) and \(\beta-\)thalassemia among pregnant women in Hubei Province, Central China

An observational study

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Abstract

There is no information concerning the prevalence of thalassemia among pregnant women in Hubei Province currently. This study is aimed to explore the prevalence of \(\alpha-\) and \(\beta-\)thalassemia genotypes among pregnant women in Hubei Province, and to explore the clinically applicable screening approach, as well as to investigate the pregnancy outcomes of \(\alpha-\) and \(\beta-\)thalassemia carriers.

Pregnant participants were recruited from 4 hospitals for the screening of \(\alpha-\) and \(\beta-\)thalassemia mutations in Hubei Province. Polymerase Chain Reaction and flow cytometry methods were used to examine \(\alpha-\) and \(\beta-\)thalassemia mutations. The hematological parameters and pregnancy outcomes of \(\alpha-\) and \(\beta-\)thalassemia carriers were obtained from the hospital information system. The chi-square tests were used to evaluate the difference in hematological parameters between pregnant thalassemia carriers and the control group.

Among 11,875 participants, 414 (3.49\%) were confirmed with \(\alpha-\)thalassemia carriers, 228 (1.92\%) were confirmed with \(\beta-\)thalassemia carriers, and 3 (0.03\%) were confirmed with both \(\alpha-\) and \(\beta-\)thalassemia carriers. The frequency of \(\alpha^{3.7}\)-thalassemia accounted for 2.05\% and it was the most frequent genotype of \(\alpha-\)thalassemia; the proportion of IVS-II-654 was 0.85\% and it was the most frequent genotype of \(\beta-\)thalassemia in Hubei Province. Furthermore, the proportion of patients with low mean corpuscular volume (MCV) or mean cell hemoglobin (MCH) values was accounted for 36.64\% and 93.97\% among \(\alpha-\)thalassemia and \(\beta-\)thalassemia carriers, respectively. And participants with normal MCV and MCH values were accounted for 95.07\% among non-thalassemia participants. High prevalence of pregnancy-induced diabetes (16.97\%), preterm birth (9.96\%), pregnancy-induced hypertension (8.12\%), and low birth weight (5.90\%) were observed among pregnant thalassemia carriers. MCV and MCH values were suggested to apply on the preliminary screening of pregnant \(\beta-\)thalassemia; however, it’s unpractical on that of \(\alpha-\)thalassemia. Furthermore, thalassemia carriers might have a high risk of negative pregnancy outcomes. These findings could be useful for the preliminary screening of thalassemia and perinatal care for the pregnant thalassemia carriers.

Abbreviations: MCH = mean cell hemoglobin, MCV = mean corpuscular volume, TI = thalassemia intermedia.

Keywords: Hubei, pregnant, prevalence, screening, thalassemia

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1. Introduction

Normal hemoglobin of hemoglobin A is a tetramer composed of a pair of α-globin chains and a pair of β-globin chains. Thalassemia is a group of diseases characterized by the reduced or deficient synthesis of one or more globin chains. As one of the most common hereditary disorders, there are great differences in the distribution of thalassemia in different areas. According to the Global Burden of Disease, the 3 countries with the highest prevalence of thalassemia mutations were Thailand (12.71%), Cambodia (12.17%), and Lao People’s Democratic Republic (11.48%) in 2019. And the prevalence of thalassemia mutations in China ranked fifth in the world (9.79%). Moreover, thalassemia was reported to be prevalent in southern China. The Li people in Hainan Province were reported to have a high prevalence of thalassemia (65.27%). According to a meta-analysis based on 16 studies in mainland China, the prevalence of β-thalassemia was 0.01% to 1.59% in Hubei Province, but there is no corresponding supportive information on the prevalence of thalassemia among pregnant women in Hubei Province currently.

In developed areas of China, thalassemia genetic screening has been regarded as one of the routine prenatal examinations, but not in most developing areas in China. As other diseases, clinical practical approaches should be promoted to generalize the thalassemia screening. Furthermore, due to advances in treatment technology, the life expectancy of thalassemia patients has been greatly increased, and patients with thalassemia static, thalassemia minor, or thalassemia intermedia (TI) have no significant effect on the overall life expectancy. However, these thalassemia patients are prone to a variety of complications, including chronic hemolytic anemia, hypoparathyroidism, cirrhosis, heart failure, pulmonary hypertension, thrombosis, and so on. Pregnant thalassemia patients might have no life-threatening symptoms, their pregnancy outcomes still warrant attention. A case-control study conducted by Vafaee et al reported that the frequency of neonates with low birth weight was significantly higher among women with β-thalassemia minor. Huang et al reported that the incidence of preterm birth and low birth weight were 6.5% and 7.3% in the thalassemia carriers. Whereas current studies focused on pregnancy outcomes among thalassemia carriers are insufficient.

For further understanding of thalassemia among pregnancies, this study is aimed to explore the prevalence of α- and β-thalassemia genotypes among pregnant women in Hubei Province, and to explore the clinically applicable screening approach, as well as to investigate the pregnancy outcomes of α- and β-thalassemia carriers.

2. Methods

2.1. Population

Hubei Province of Central China has 13 prefecture-level administrative regions and 4 county-level administrative regions. The Eastern region includes Huangshi City, Ezhou City, Huanggang City, Xiangning City, and Xiaogan City; the Central region includes Wuhan City, Jingzhou City, Jingmen City, and the county-level administrative regions; the Western region includes Yichang City, Shiyan City, Xiangyang City, Suizhou City, and Enshi City. This study was approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province on Sep 3, 2018. In this study, 4 hospitals providing medical services for patients mainly from the Eastern, Central, and Western regions of Hubei Province were selected. Pregnant women were recruited in these hospitals to participate in the screening of α- and β-thalassemia mutations from January 2019 to November 2020, and they were further classified by residence address. The least sample size in this study was calculated by the following determination formulas: \( n = \frac{t^2 \times \bar{P}(1-\bar{P})}{d^2} \), \( t = 1.96 \), \( P = 4\% \), \( d = 0.4\% \), \( n \approx 9220 \), and the current study recruited a total of 11,875 eligible participants.

2.2. Genetic analysis

In this study, thalassemia (α/β) Gene Diagnostic Kit (Polymerase Chain Reaction [PCR]-Flow cytometry fluorescence Hybridization Assay) was used to detect thalassemia genotypes. PCR primers and hybridization probes were designed for the hot spots of thalassemia mutation. A total of 20 point-mutations includes 3 α-mutations (WS122, QS125, and CS142) and 17 β-mutations (CD41-42, IVS-II-654, CD17-28, CD26, CD71-72, CD43-29, Int, CD14-15, CD27-28, –32, –30, IVS-I-1, IVS-I-5, CD31, and CAP). Moreover, a total of 3 deletion mutations (–sea, –α3.7, and –α4.2) and 1 normal controlling genotype were amplified. PCR and flow cytometry methods were used to examine α- and β-thalassemia mutations.

2.3. Data collection and analysis

The prevalence of different thalassemia alleles among pregnant women was described in Hubei Province stratified by East, Central, and West. The hematological parameters including red blood cell, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean cell hemoglobin (MCH), and mean corpuscular hemoglobin concentration were collected. Thalassemia carriers with a singleton pregnancy were selected to follow up for pregnancy outcomes including preterm birth, pregnancy-induced hypertension, pregnancy-induced diabetes, eclampsia/preeclampsia, birth defect, miscarriage, stillbirth, fetal weight, and Apгар scores. Data of the hematological parameters and pregnancy outcomes were obtained from the hospital information system. The chi-square tests were used to evaluate the difference in hematological parameters between α- and β-thalassemia carriers. Statistical analysis was conducted with SAS 9.4 (SAS Institute, Cary, NC, USA) for Windows. Two-sided P values <.05 were considered statistically significant.

3. Results

Among the 11,875 participants, 8150 (68.63%) provided the hematological parameters, 645 (5.43%) were diagnosed with thalassemia carriers, and 271 (42.02%) of the singleton thalassemia carriers were tracked with a pregnancy outcome in this study.

A total of 23 genotypes and 17 gene mutations of α- and β-thalassemia were identified. Among the thalassemia carriers, 414 (3.49%) were confirmed with α-thalassemia carriers, 228 (1.92%) were confirmed with β-thalassemia carriers, and 3 (0.03%) were confirmed with both α- and β-thalassemia carriers (Table 1). Three types of α-thalassemia static including –α3.7, –α4.2, and α-W accounted for 69.81% of α-thalassemia carriers, and more details were provided in Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A885. The frequency of –α3.7 accounted for 2.05% and it was the most frequent genotype accounting for more than half of the α-thalassemia among Eastern, Central, and Western of Hubei Province.
followed by $-\alpha^{3.7}$ (static) (0.94%) and $-\alpha^{4.2}$ (0.31%) genotypes. Three cases of $2\alpha$-globin mutations including $-\alpha^{3.7}$, $-\alpha^{4.2}$, $-\alpha^{4.2}$ SE/A, WS, and $\alpha^{CS}$-$\alpha^{3.7}$ were identified.

The prevalence of IVS-II-654 accounted for 0.85% and it was the most frequent genotype of $\beta$-thalassemia in the Eastern, Central, and Western of Hubei Province. Other high prevalence $\beta$-thalassemia genotypes were CD41-42 (0.37%), CD17 (0.34%), and CD27-28 (0.12%). Different from Eastern Hubei and Western Hubei, CD17 accounted for 19.51% and it ranked second among all of the $\beta$-thalassemia genotypes in Central Hubei. Moreover, 1 TI case of $-\alpha^{3.7}$, IVS-II-654 combined with $-\alpha^{3.7}$, and CD71-72 combined with $\alpha^{3.7}$

Table 2 shows that there were 11.83% and 12.07% of $\alpha$- and $\beta$-thalassemia carriers and $\alpha$-thalassemia carriers suffering from low red blood cell (<3.8 10^{12}/L), respectively. The majority of $\beta$-thalassemia carriers showed low hemoglobin (<110 g/L) (84.48%) and hematocrit (<0.35) (81.90%). Only 34.73% of $\alpha$-thalassemia carriers were detected with low MCV (<82 fl), while corresponding proportion was 93.97% among $\beta$-thalassemia carriers. The $\beta$-thalassemia carriers also showed a higher proportion of low MCH (<27 pg) than that of $\alpha$-thalassemia carriers (93.97% vs 35.88%). There were 93.97% and 36.64% of $\beta$-thalassemia carriers and $\alpha$-thalassemia carriers presented low MCV or MCH, respectively. Meanwhile, 97.47% of non-thalassemia carriers presented normal MCV and MCH.

Table 3 shows that the most prevalent complication of pregnant thalassemia carriers was pregnancy-induced diabetes (16.97%), followed by preterm birth (9.96%). Pregnancy-induced hypertension was also prevalent among $\alpha$-thalassemia carriers (10.16%). The prevalence of eclampsia or preeclampsia was 2.95% among all of the thalassemia carriers. For neonatal outcomes, neonates with 1-minute Apgar scores <10 points comprised a proportion of 15.50%. Low birth weight neonates accounted for 5.88% and 5.95% among both $\alpha$- and $\beta$-thalassemia carriers, respectively. The prevalence of birth defects among $\alpha$- and $\beta$-thalassemia carriers accounted for 2.14% and 4.76%, respectively.

4. Discussion

This study firstly reported the frequency of $\alpha$- and $\beta$-thalassemia carriers among pregnant women in Hubei Province, which was lower than the prevalence of thalassemia carriers among the general population of Chongqing (7.76%) and Shenzhen (6.49%) and this gap could be explained by the difference of targeted populations.

Moreover, this study presented the proportion of $-\alpha^{3.7}$ genotype ranked the first among all the $\alpha$-thalassemia genotypes, in line with Chongqing China, Northern Thailand, and Southwest Iran. Diejomaoh et al. also confirmed that $-\alpha^{3.7}$ was the commonest $\alpha$-thalassemia allele in the pregnant Kuwaiti population. Additionally, $-\alpha^{3.7}$ was another common genotype that accounted for 27.05% of all $\alpha$-thalassemia mutations in this study. However, $-\alpha^{3.7}$ was previously reported to be the most frequent $\alpha$-thalassemia genotype in China. Additionally, this study only included 1 case of TI who was...
diagnosed with Hemoglobin H disease. In prenatal diagnosis genetic counseling, mothers with \( \text{SEA/\alpha WS} \) genotype can be exempted from prenatal diagnosis similarly to \( \text{SEA/aa} \) genotype.\cite{23}

In line with our result, Cai et al.\cite{21} focused on the prevalence of \( \beta \)-thalassemia genotypes and confirmed that the 3 most common \( \beta \)-thalassemia genotypes were IVS-II-654, CD41-42, and CD17 among neonates in Wuhan, Hubei Province. The proportion of different \( \beta \)-thalassemia genotypes in Eastern, Central, and Western areas were inconsistent, which might be explained by the unbalanced distribution of the floating population in Hubei Province. Central Hubei has a large number of floating populations than Eastern and Western areas, and the migrant population was confirmed to be one of the important factors in the prevalence of thalassemia.\cite{24}

The sensitivity of low MCV or MCH values on the \( \beta \)-thalassemia screening was 93.97% in this study, which further confirmed that MCV and MCH values are reliable on the first step screening of \( \beta \)-thalassemia.\cite{25} Phanmany et al.\cite{26} recommended that MCV and MCH values are regarded as important indicators in the first step of both \( \alpha \)- and \( \beta \)-thalassemia screening. Whereas the proportion of pregnant \( \alpha \)-thalassemia carriers with decreased MCV or MCH in this study were only 34.73% and 35.88%, respectively. As reported previously, most \( \alpha \)-thalassemia static carriers have normal hematological characters.\cite{27} In this study, pregnant \( \alpha \)-thalassemia static carriers comprised a high proportion of 69.81%, and little \( \alpha \)-thalassemia static carriers were detected with MCV < 82 (9.09%) or MCH < 27 (10.70%) (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A885). Thus, it's not appropriate to use MCV and MCH values on the preliminary screening of pregnant \( \alpha \)-thalassemia carriers. These results could be contributed to generalizing the thalassemia screening in perinatal care.

This study showed a high rate of negative pregnancy outcomes among thalassemia carriers, compared with general pregnant women.\cite{28} Thame et al.\cite{29} announced that infants of mothers

**Table 2**

The hemotological parameters among pregnant thalassemia carriers and control group.

| Variables | \( \alpha \)-thalassemia N (%) | \( \beta \)-thalassemia N (%) | None-thalassemia N (%) | \( \chi^2 \) | \( P \) |
|-----------|-------------------------------|-------------------------------|------------------------|---------|-------|
| RBC, 10^9/L |                               |                               |                        |         |       |
| < 3.8     | 31 (11.83)                     | 14 (12.07)                    | 2310 (29.72)           | 54.15   | <.001 |
| ≥ 3.8     | 231 (88.17)                    | 102 (87.93)                   | 5462 (70.28)           |         |       |
| HGB, g/L  |                               |                               |                        |         |       |
| < 110     | 55 (20.99)                     | 98 (84.48)                    | 654 (8.41)             | 281.57  | <.001 |
| ≥ 110     | 207 (79.01)                    | 18 (15.52)                    | 7118 (91.59)           |         |       |
| HCT, L/L  |                               |                               |                        |         |       |
| < 0.35    | 65 (24.81)                     | 95 (81.90)                    | 1348 (17.34)           | 95.14   | <.001 |
| ≥ 0.35    | 197 (75.19)                    | 21 (18.10)                    | 6424 (82.66)           |         |       |
| MCV, fl   |                               |                               |                        |         |       |
| < 82      | 91 (34.73)                     | 109 (93.97)                   | 129 (1.66)             | 1938.71 | <.001 |
| ≥ 82      | 171 (65.27)                    | 7 (6.03)                      | 7643 (98.34)           |         |       |
| MCH, pg   |                               |                               |                        |         |       |
| < 27      | 94 (35.88)                     | 109 (93.97)                   | 181 (2.33)             | 1688.67 | <.001 |
| ≥ 27      | 168 (64.12)                    | 7 (6.03)                      | 7591 (97.67)           |         |       |
| MCHC, g/L |                               |                               |                        |         |       |
| < 316     | 50 (19.08)                     | 55 (47.41)                    | 193 (2.48)             | 522.73  | <.001 |
| ≥ 316     | 212 (80.92)                    | 61 (52.59)                    | 7579 (97.52)           |         |       |
| MCV < 82 and/or MCH < 27 |         |                               |                        |         |       |
| Yes       | 96 (36.64)                     | 109 (93.97)                   | 197 (2.53)             | 1643.75 | <.001 |
| No        | 166 (63.36)                    | 7 (6.03)                      | 7575 (97.47)           |         |       |

HCT=hematocrit, HGB=hemoglobin, MCH=mean cell hemoglobin, MCHC=mean corpuscular hemoglobin concentration, MCV=mean corpuscular volume, RBC=red blood cell.

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**Table 3**

Pregnancy outcomes of \( \alpha \)- and \( \beta \)-thalassemia carriers.

| Variables             | \( \alpha \)-thalassemia N (%) | \( \beta \)-thalassemia N (%) | Total N (%) |
|-----------------------|-------------------------------|-------------------------------|-------------|
| Maternal outcomes     |                               |                               |             |
| Pregnancy-induced diabetes | 31 (16.58)                    | 15 (17.86)                    | 46 (16.97)  |
| Preterm birth         | 19 (10.16)                     | 8 (9.52)                      | 27 (9.96)   |
| Pregnancy-induced hypertension | 19 (10.16) | 3 (3.57) | 22 (8.12) |
| Eclampsia or preeclampsia | 7 (3.74)                      | 1 (1.19)                      | 8 (2.95)    |
| Neonatal outcomes     |                               |                               |             |
| 1-minute Apgar scores < 10 | 29 (15.51)                    | 13 (15.48)                    | 42 (15.50)  |
| 5-minute Apgar scores < 10 | 4 (2.14)                     | 4 (4.76)                      | 8 (2.95)    |
| Fetal weight < 2500   | 11 (5.88)                     | 5 (5.95)                      | 16 (5.90)   |
| Fetal weight > 4000   | 9 (4.81)                      | 1 (1.19)                      | 10 (3.69)   |
| Birth defect          | 4 (2.14)                      | 4 (4.76)                      | 8 (2.95)    |
| Miscarry              | 1 (0.53)                      | 0                             | 1 (0.37)    |
| Stillbirth            | 0                             | 1 (1.19)                      | 1 (0.37)    |
with homozygous sickle cell disease might have a higher risk of poor pregnancy outcomes. It is noticeable that the proportion of pregnancy-induced diabetes was as high as 16.58% and 17.86% among pregnant α- and β-thalassemia carriers, respectively, which was largely higher than what was reported in thalassemia major patients (6.54–9.0%).

Another study focused on Chinese populations reported that the prevalence of diabetes was 1.90% (4/211) among patients with non-transfusion-dependent thalassemia. Attention should be paid to pregnancy-induced diabetes in thalassemia patients.

It should also be noted that α-thalassemia carriers might have worse pregnancy outcomes compared with β-thalassemia, especially for pregnancy-induced hypertension and eclampsia/ preeclampsia. The frequency of pregnancy-induced hypertension among pregnant α-thalassemia was close to what was reported in China (8.60–11.95%). However, it was much lower among pregnant β-thalassemia carriers. Serum cholesterol levels, blood viscosity, or arterial blood pressure, which were positively related with pregnancy-induced hypertension, were lower in β-thalassemia carriers compared with α-thalassemia carriers. Moreover, this study presented significantly decreased levels of hematological indicators including MCV and MCH among β-thalassemia carriers as mentioned above. The mechanism of the associations between α- and β-thalassemia and pregnancy outcomes needs further study.

This study has several limitations. First, this study only examined the thalassemia gene mutations and focused on the prevalence, screening, and pregnancy outcomes among pregnant women, but the hereditism of thalassemia was not examined. Second, this study only detected 17 common gene mutations; other rare mutations were not examined. Third, the prevalence of thalassemia carriers among different nations in Hubei Province was not examined in this study. Fourth, due to the high rate of lost follow-up, this study only collected the pregnancy outcomes of thalassemia carriers instead of all the participants including the control group.

5. Conclusion

This study filled the gap in the prevalence of α- and β-thalassemia carriers among pregnant women in Hubei Province. MCV and MCH values were suggested to apply on the first step of β-thalassemia screening; however, it might be unpractical on the preliminary screening of pregnant α-thalassemia carriers, among whom genetic screening is recommended as a priority. Furthermore, thalassemia carriers might have a high risk of negative pregnancy outcomes, and further study focused on the impact of thalassemia on the pregnancy outcomes is promoted in the future. These findings could be useful for the preliminary screening of thalassemia and perinatal care for the pregnant thalassemia carriers.

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References

[1] Global Burden of Disease. Thalassemia trait, Both sexes, All ages, Percent of total prevalent cases; 2019. Available at: https://vizhub.healthdata.org/gbd-compare/. Accessed Jan 19, 2021.

[2] Tang W, Zhang C, Lu F, et al. Spectrum of α-thalassemia and β-thalassemia mutations in the Guilin Region of southern China. Clin Biochem 2015;48:1068–72.

[3] He S, Li J, Li DM, et al. Molecular characterization of α- and β-thalassemia in the Yulin region of Southern China. Gene 2018;653:61–4.

[4] Yao H, Chen X, Lin L, et al. The spectrum of α- and β-thalassemia mutations of the Li people in Hainan Province of China. Blood Cells Mol Dis 2014;53:16–20.

[5] Lai K, Huang G, Su L, He Y. The prevalence of thalassemia in mainland China: evidence from epidemiological surveys. Sci Rep 2017;7:920.

[6] Agasalda-Garcia M, Shieh T, Souza R, et al. Raman-Enhanced Spectroscopy (RESpect) probe for childhood non-hodgkin lymphoma. SciMed J 2020;2:1–7.

[7] Osipov M, Sokolnikov M. Previous malignancy as a risk factor for the second solid cancer in a cohort of nuclear workers. SciMed J 2021;3:8–15.

[8] Graffeo L, Vitrano A, Scondotto A, et al. β-Thalassemia heterozygote state detrimentally affects health expectation. Eur J Intern Med 2018;54:76–80.

[9] Sayani FA, Kwiatkowski JL. Increasing prevalence of thalassemia in America: implications for primary care. Ann Med 2015;47:592–604.

[10] Ngim CF, Lee MY, Othman N, Lim SM, Ng CS, Ramadas A. Prevalence and risk factors for cardiac and liver iron overload in adults with thalassemia in Malaysia. Hemoglobin 2019;43:95–100.

[11] Basha NK, Shetty B, Shenoy UV. Prevalence of hypophosphatridism (HPT) in beta thalassemia major. J Clin Diagn Res 2014;8:24–6.

[12] Moghadhdam HM, Badiei Z, Eftekhari K, Shakkeri R, Farhangi H. Prevalence of pulmonary hypertension in patients with thalassemia intermedia in 2009: a single center’s experience. Electron Physician 2015;7:1102–7.

[13] Vafaie H, Karimi S, Jahromi MA, Asadi N, Kasraeean M. The effect of mother’s β-thalassemia minor on placental histology and neonatal outcomes. J Matern Fetal Neonatal Med 2020;29:120–4.

[14] Huang XC, Qiu XQ, Zeng XY, et al. Associations of parental thalassemia with preterm birth and low birth weight. Chin J Epidemiol 2019;40:596–600. (in Chinese).

[15] Yao XY, Yu J, Chen SP, et al. Prevalence and genetic analysis of α-thalassemia and β-thalassemia in Chongqing area of China. Gene 2013;532:120–4.

[16] Li Z, Li F, Li M, Guo R, Zhang W. The prevalence and spectrum of thalassemia in Shenzhen, Guangdong Province, People’s Republic of China. Hemoglobin 2006;30:9–14.

[17] Yu J, Xian Y, Yao X, et al. Prevalence and molecular analysis of α-thalassemia in preschool children in Chongqing city. Chin J Hematol 2014;35:419–23. (In Chinese).

[18] Lithanatudom P, Khampan P, Smith DR, et al. The prevalence of alpha-thalassemia amongst Tai and Mon-Khmer ethnic groups residing in northern Thailand: a population-based study. Hematology 2016;21:480–5.

[19] Nezhad FH, Nezhad KH, Choghakabodi PM, Keikhaie B. Prevalence and genetic analysis of α- and β-thalassemia and sickle cell anemia in Southwest Iran. J Epidemiol Glob Health 2018;8:189–95.
[20] Diejomaoh FM, Haider MZ, Dalal H, Abdulaziz A, D’Souza TM, Adekile AD. Influence of alpha-thalassemia trait on the prevalence and severity of anemia in pregnancy among women in Kuwait. Acta Haematol 2000;104:92–4.

[21] Cai W, Xiong Q, Tong J, et al. Prevalence and genetic analysis of thalassemia in neonates in Wuhan area: a national megacity in central China. J Matern Fetal Neonatal Med 2019;11:1–8.

[22] Huang SW, Xu Y, Liu XM, et al. The prevalence and spectrum of α-Thalassemia in Guizhou Province of South China. Hemoglobin 2015;39:260–3.

[23] Zhang S, Xiao Q, Chen B, et al. Genotype and hematological phenotype analysis of α-thalassemia hemoglobin H disease. Chin J Lab Med 2020;43:1232–6. (in Chinese).

[24] Li B, Zhang XZ, Yin AH, et al. High prevalence of thalassemia in migrant populations in Guangdong Province, China. BMC Public Health 2014;14:905.

[25] Singha K, Taweenan W, Fucharoen G, Fucharoen S. Erythrocyte indices in a large cohort of β-thalassemia carrier: implication for population screening in an area with high prevalence and heterogeneity of thalassemia. Int J Lab Hematol 2019;41:513–8.

[26] Phannany S, Chanprasert S, Munkongdce T, Svasti S, Leecharoenkhat K. Molecular prevalence of thalassemia and hemoglobinopathies among the Lao Loum Group in the Lao People’s Democratic Republic. Int J Lab Hematol 2019;41:650–6.

[27] Youssry I, El Badawy A, Samy RM, Salama N, Abd Elaziz D, Rizk S. Prevalence of α-Thalassemia in the Egyptian population. Hemoglobin 2018;42:243–6.

[28] Luo J, Fan C, Luo M, Fang J, Zhou S, Zhang F. Pregnancy complications among nulliparous and multiparous women with advanced maternal age: a community-based prospective cohort study in China. BMC Pregnancy Childbirth 2020;20:581.

[29] Thame M, Lewis J, Trotman H, Hambleton I, Serjeant G. The mechanisms of low birth weight in infants of mothers with homozygous sickle cell disease. Pediatrics 2007;120:e686–93.

[30] Ho LN, Chen W, Yang Y, et al. Elevated prevalence of abnormal glucose metabolism and other endocrine disorders in patients with β-thalassemia major: a meta-analysis. Biomed Res Int 2019;2019:6573497.

[31] Azami M, Sharifi A, Norouzi S, Mansouri A, Sayehmiri K. Prevalence of diabetes, impaired fasting glucose and impaired glucose tolerance in patients with thalassemia major in Iran: a meta-analysis study. Caspian J Intern Med 2017;8:1–15.

[32] Luo Y, Bajoria R, Lai Y, et al. Prevalence of abnormal glucose homeostasis in Chinese patients with non-transfusion-dependent thalassemia. Diabetes Metab Syndr Obes 2019;12:457–68.

[33] Li N, An H, Li Z, et al. Preconception blood pressure and risk of gestational hypertension and preeclampsia: a large cohort study in China. Hypertens Res 2020;43:956–62.

[34] Karimi M, Marvasti VE, Motazedian S, Sharifian M. Is beta-thalassemia trait a protective factor against hypertension in young adults? Ann Hematol 2006;85:29–31.

[35] Gallerani M, Scapoli C, Cicognani I, et al. Thalassaemia trait and myocardial infarction: low infarction incidence in male subjects confirmed. J Intern Med 1991;230:109–11.