J Chin Med Assoc

ORIGINAL ARTICLE

Sickle cell anemia in pregnant Saudi women and its impact on birth weight and gestational maturity

Ebtihal Elameen Eltyeb[a,*], Alanoud Ibrahim Mokhasha[b], Ali Ali Al-Makramani[a], Maha Murtada Abdelmageed[c], Randa Amin Basheer[d]

[a]Department of Paediatrics, Faculty of Medicine, Jazan University, Jazan, Saudi Arabia; [b]Family Medicine Program at Jazan, Saudi Arabia; [c]Department of Obstetrics and Gynaecology, Faculty of Medicine, Jazan University, Saudi Arabia; [d]Department of Nursing, Farasan University College, Jazan University, Saudi Arabia

Abstract

Background: It is well documented that sickle cell anemia (SCA) in pregnancy increases the risk of problems that can influence the growth and maturation of the newborn. To assess the gestational maturity and birth weight of babies born to Saudi mothers with SCA in the Jazan region.

Methods: A case-control study was conducted in three hospitals in the Jazan region. An interview with a semi-structured questionnaire was used to collect data from the participants' women, and then the birth weight was taken.

Results: Of 187 delivered women, 20.3% had SCA (13% had sickle cell disease, and the remaining had sickle cell trait). Among the 38 affected mothers, 15.7% were considered to have an additional risk (7.9% had diabetes mellitus, 5.3% had hypertension, and 2.6% were smokers). The mean birth weight was 2.95 ± 0.40 kg and 2.99 ± 0.55 kg in the case and control groups, respectively. However, the low birth weight babies constitute 31% of the delivered babies in the SCA group with a weight of 2.33 ± 0.16 kg and 15% of the control group with a mean weight of 2.16 ± 0.30 kg. The gestational age was 39.36 ± 1.02 weeks in the SCA group compared to 39.5 ± 1.17 weeks in the control group. Maternal age and hypertension significantly influence the birth weight in the SCA group compared to the influence of diabetes mellitus on the birth weight in the control group.

Conclusion: This study indicates that SCA in pregnant mothers influences birth weight, which is more impacted by maternal age and co-morbidities. Therefore, a multidisciplinary approach must monitor these risky pregnancies well to avoid undesirable neonatal outcomes.

Keywords: Birth weight; Gestational maturity; Neonatal outcome; Saudi mothers; Sickle cell anemia

1. INTRODUCTION

Sickle cell anemia (SCA) is a condition brought on by faulty mutant hemoglobin production that leads to tissue ischemia and infarction throughout the body in SCA patients. SCA is the most prevalent hemoglobinopathy during pregnancy that might cause prematurity and low birth weight (LBW).[1,2] Other maternal factors, such as dietary status, smoking, and drug use, as well as fetal and placental factors, such as genetic makeup, affect fetal growth and add more risks and adverse neonatal outcomes in mothers with SCA.[3,4] In addition, SCA mothers experience an aggravation of the physiological changes of pregnancy, such as an increase in metabolic demand, blood viscosity, and hypercoagulability, which increases the risk of complications like a vaso-occlusive crisis and thrombo-embolic events.[5]

The most frequent pathophysiologic cause of fetal growth retardation in a healthy pregnancy is placental insufficiency, which occurs when the fetus cannot grow to its total capacity due to decreased placental function.[6,7] As a consequence of SCA, vaso-occlusion in the placenta causes villous fibrosis, necrosis, and infarction, impairs uteroplacental circulation, and results in prolonged fetal hypoxia and unfavorable fetal outcomes.[8,9] Previous research on the prognosis of pregnancy in women with SCA showed an almost universally unfavorable outcome for mothers and children. However, preconception care and other advances in medical care have significantly improved the situation.[2] Additionally, gestational diabetes is another maternal risk that is observed to be highly related to pregnancy in SCA; also, these mothers have an increased risk of spontaneous miscarriages and stillbirths due to micro-vascular damage and reduced uteroplacental circulation.[10]

The prevalence of SCA in Saudi Arabia varies wildly in different parts of the country, with the highest prevalence in the Eastern province, followed by the southwestern provinces.[11] According to the Saudi Premarital Screening Program, the adult population has a sickle cell gene prevalence of 4.2% for sickle cell trait and 0.26% for sickle cell disease.[12,13] The current study aimed to assess neonatal maturity and birth weight as outcomes in neonates delivered to mothers with SCA in the Jazan region and to assess the association between demographic variables of the mothers affected with SCA and neonatal outcomes.

*Address correspondence. Dr. Ebtihal Elameen Eltyeb, Department of Paediatrics, Jazan University, P.O. Box: 2349. Postal Code: 82621, Jazan, Saudi Arabia. E-mail addresses: bebotyb@gmail.com, eeltyeb@jazanu.edu.sa (E. E. Eltyeb).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2023) 86: 892-896.

Received May 24, 2023; accepted July 14, 2023.

doi: 10.1097/JCMA.0000000000000974.

2. METHODS

2.1. Context of the study

A case-control study was conducted and targeted both women, with SCA (case group) and non-SCA (control group), after delivery and newborn babies in three hospitals (Sabia, Sametah, Abu Arish General Hospital) in the Jazan region, reflecting the population in north, east, and west region of Jazan region respectively. Jazan region lies in southwestern Saudi Arabia, north of Yemen, with a population of 1.6 million.[14]

2.2. Data collection tool

The data collection tool included a semi-structured questionnaire within the context of a direct interview. The questionnaire was designed in Arabic to enable a more straightforward data collection process from the targeted population. It was designed to assess maternal data and neonatal birth outcomes. The demographic data included the mother's age, educational level, occupation, and residence. In addition, the mother's other maternal risk factors were considered, like hypertension, diabetes mellitus, smoking, and using medications during pregnancy. Also, questions to assess antenatal care were included in the form of easy access to service and the frequency of visits. Finally, data related to neonatal birth outcomes were collected to evaluate the mode of delivery, gestational age, baby gender, and birth weight. Some case definitions were used in this study and should be mentioned in this context: *maturity* is defined as birth after the completion of 37 weeks of gestation.[15] *LBW* was represented as a birth weight of <2500 g, while *high birth weight* was defined as a birth weight of more than 4000 g.[16,17]

2.3. Data collection process and the participants

This study targeted women with a history of SCA in the Jazan region compared with non-SCA women who delivered in the same hospitals and region. All Saudi mothers delivered in the target hospitals were included in this study; the mothers who refused to participate were excluded. In order to determine the sample size, a case-control ratio of 1:4 was used. In other words, we included approximately four mothers of control babies for every mother of a case group. The data were collected through personal interviews using a self-developed questionnaire after verbal informed consent was obtained before the interviews were initiated. Data were collected from the participants under a guarantee of anonymity—no identification data were gathered. Interviews were performed in private settings to ensure the privacy of participating women. Then the weight of the delivered newborn was obtained in kilograms (kg) using the weight scales in the delivery rooms shortly after delivery. A comparison group of 149 women with an AA phenotype hemoglobin, matched as closely as possible regarding maternal age and the delivery date, was included in the study, along with 38 singleton-delivered women with SCA (diseased: SS phenotype and trait: SA phenotype).

2.4. Data analysis

Data were analyzed via the Statistical Package for Social Sciences software, version 23.0 (IBM SPSS Inc., Chicago, IL). All information was gathered via a questionnaire and coded into variables. Categorical variables were shown as numbers and ratios, while continuous variables were shown as mean and standard deviation. Comparing proportions was done using the chi-square test; means were compared using the Student t-test. To estimate the relationship between the two variables, the odds ratio with a 95% confidence interval was generated. A value of less than 0.05 was considered significant for the probability value. To find the linked factors with the most significant power and to get rid of the ones that confused, logistic regression was used.

3. RESULTS

During the study period, there were 38 deliveries of pregnant SCA women. More than half of them aged ranged between 20 and 30 years old. Thirty-five percent were university educated, 78 percent were non-workers, and about 75 percent of the women came from rural areas. Eighty-six percent of the study sample diagnosed sickle cell trait with hemoglobin phenotype SA. Compared to 149 non-SCA women, the control group matched the SCA group in age and residence with almost a percentage distribution of age, residence, and education variables.

Regarding the variables in the two groups, 2.6% of SCA groups were smokers, 7.9% were diabetic, and 5.3% were hypertensive. These compared to 2% smokers, 6.7% diabetic, and 6.7% hypertensive in the control group. The antenatal care was adequate in two groups, constituting 89% in the case group and 75 % in the control group, as shown in Table 1. The mode of delivery was vaginal deliveries in more than 70% of the case and control groups, while the birth weight was 2.95 $\pm$ 0.40 kg and 2.99 $\pm$ 0.55 kg in the case group and control group, respectively. However, the LBW babies constitute 31% of the delivered babies in the SCA group with a weight of 2.33 $\pm$.16 kg and 15% of the control group with a mean weight of 2.16 $\pm$ 0.30 kg. In addition, the gestational age was 39.36 $\pm$ 1.02 weeks in the case group compared to 39.5 $\pm$ 1.17 weeks in the control group, as demonstrated in Table 2.

Using the correlation tests as shown in Table 3 to assess the influence of the different variables on the birth weight, there is a significant influence of maternal age and if the mother diagnosed with high blood pressure on the birth weight in the SCA group compared to the influence of the diabetes mellitus on the birth weight in the control group. In addition, Table 4 shows a significant correlation between the mother diagnosed with diabetes mellitus and the gestational age in the control group. At the same time, there is no significant correlation between the variables and the gestational age in the case group.

4. DISCUSSION

In this study, most participant mothers in the SCA group were sickle cell trait (86.8%), 15.7% of the group was considered to have additional risk factors as 7.9% had diabetes mellitus, 5.3% were hypertensive, and 2.6% were smokers as in Table 1. The overall birth weight distribution was average compared to the control group, which showed 2.95 $\pm$ 0.40 kg and 2.99 $\pm$ 0.55 kg in the case and control groups, respectively. However, the percentage of LBW is considerably increased in the SCA group (31%) compared to the control group, as shown in Table 2. It is well documented that the lower birth weight in babies of mothers with SCA is significantly associated with lower gestational age and placental weight.[18,19] The study findings suggest that infants born to mothers with SCA have a higher chance of LBW than infants born without SCA. This result can be attributed to factors such as placental insufficiency due to vaso-occlusion, which impairs uteroplacental circulation and leads to fetal hypoxia. Other complications associated with SCA, such as pre-eclampsia, infections, and intrauterine growth retardation, can also contribute to adverse neonatal outcomes.[19–21] The result of our study agreed with the studies that reported that newborns born to mothers with the sickle cell trait were significantly smaller than babies born to mothers in a similar group with normal hemoglobin genotype.[22,23] Although most participants in the study had sickle cell trait rather than sickle cell disease, there were still a significant proportion of LBW infants in the SCA group. The impact of the sickle cell trait on birth weight and gestational maturity remains debatable, as some investigations

Table 1

Sickle cell anemia patients and control group characteristics

		SCA group (n = 38)		Control group (n = 149)	
Variables		Frequency	%	Frequency	%
Mother age	20-30	21	56.8	96	64.4
	31-40	13	35.1	49	32.9
	41-50	4	8.1	4	2.7
Mother's education	Not educated	8	21.1	37	24.8
	Primary	7	18.4	18	12.1
	intermediate	1	2.6	14	9.4
	Secondary	9	23.7	34	22.8
	University	13	34.2	46	30.9
Mother's occupation	Non-worker	30	78.9	127	85.2
	Worker	8	21.1	22	14,8
Region	Sabya	3	7.9	19	12.8
	Samtah	10	26.3	50	33.6
	Abu Arish	4	10.5	40	26.8
	Alardah	10	26.3	6	4.0
	Ahed Almsarha	3	7.9	7	4.7
	Damad	3	7.9	3	2.0
	Jazan	1	2.6	2	1.3
	others	4	10.5	22	14.8
Residence	Urban	9	23.7	30	20.1
	Rural	29	76.3	119	79.8
If the mother smoke	Yes	1	2.6	3	2.0
	No	37	97.4	146	98.0
If the mother diagnosed with hypertension	Yes	2	5.3	10	6.7
	No	36	94.7	139	93.3
If the mother diagnosed with diabetes mellitus	Yes	3	7.9	10	6.7
	No	35	92.1	139	93.3
The type of sickle cell anemia	SCD	5	13.2	13.5	-
	SCT	33	86.8	100.0	-
If the mother receive medications during pregnancy	Yes	16	40.5	37	31.1
	No	22	59.5	112	24.8
Regular antenatal visits	Yes	34	89.5	128	75.2
	No	4	10.5	21	14.1

SCD = sickle cell disease; SCT = sickle cell trait.

Table 2

Neonatal outcomes in sickle cell anemia patients and control groups

	SCA group (n =38)			Control group (n = 149)		
Outcomes	**Mean ± SD**	**Minimum**	**Maximum**	**Mean ± SD**	**Minimum**	**Maximum**
Birth weight (kg)	2.9474 ± 0.40	2.00	3.90	2.99 ± 0.55	1.00	5.00
LBW	2.33 ± 0.16 kg	N: 12 (31.6%)		2.16 ± 0.3 kg	N: 23 (15.44%)	
Gestational age (weeks)	39.36 ± 1.02	37.00	40.00	39.5 ± 1.17	34.00	42.00
Gestational age < 37 weeks		N: 0 (0%)			N: 1 (0.67%)	
Mode of delivery	Vaginal	29 (76.3%)		Vaginal	105 (70.5%)	
	Cesarean	9 (23.7%)		Cesarean	44 (29.5%)	
Gender	Male	22 (57.9%)		Male	81 (54.4%)	
	Female	16 (42.1%)		Female	68 (45.6)	

LBW = low birth weight.

indicate that babies born to mothers with the trait may develop normally.[24,25]

Antenatal care is essential to maternal and newborn well-being, specifically in SCA mothers. In this study, although there was no direct correlation between antenatal care and birth weight or gestational maturity, the mothers demonstrated a good percentage of regular visits during their pregnancy. Ideally, a thorough evaluation needs to be done during the initial prenatal appointment, and the mothers should be informed of the importance of routine antenatal care; throughout the first two trimesters, Because these women are more likely to have pre-eclampsia and have a more increased risk of developing infections.[26,27] Also, mothers should be warned about the dangers of over-exertion, dehydration, and exposure to severe temperatures, which can lead to sickle cell crises. Moreover, women with a higher risk of developing pre-eclampsia should take low-dose aspirin during pregnancy.[28,29]

The current study emphasizes the importance of addressing maternal risk factors, such as hypertension and diabetes mellitus, in managing SCA pregnancies. These factors significantly

Table 3

Correlation between variables and birth weight in SCA group and control group

	SCA group (n = 38)			Control group (n =149)		
variables	**Value**	**df**	**Significance (2-sided)**	**Value**	**df**	**Significance (2-sided)**
Mother age	339.537	260	0.001	707.627	672	0.165
Mother education	41.246	52	0.880	97.270	95	0.445
Mother occupation	8.919	13	0.779	28.169	24	0.253
Region	77.527	91	0.842	195.863	168	0.070
If have regular antenatal care visits	19.714	13	0.103	151.50	24	0.916
If the mother smoke	8.730	13	0.793	28.058	24	0.258
If the mother diagnosed with hypertension	38.000	13	0.000	14.260	24	0.941
If the mother diagnosed with diabetes mellitus	19.663	13	0.104	43.678	24	0.008
If the mother had any other chronic illness	5.477	13	0.963	72.932	48	0.012
If the mother receive any medication during the pregnancy	12.654	13	0.475	23.078	24	0.515
If the mother SCA diseased or carrier	16.121	13	0.243	-	-	-

Table 4

Correlation between variables and gestational age in SCA group and control group

	SCA group (n = 38)			Control group (n = 149)		
variables	**Value**	**df**	**Significance (2-sided)**	**Value**	**df**	**Significance (2-sided)**
Mother age	76.752	60	0.071	196.642	168	0.065
Mother education	19.484	12	0.078	16.369	24	0.874
Mother occupation	2.903	3	0.407	4.825	6	0.566
Region	33.630	21	0.040	39.308	42	0.590
If have regular antenatal care visits	2.537	3	0.469	6.298	6	0.391
If the mother smoke	0.534	3	0.911	5.386	6	0.495
If the mother diagnosed with hypertension	1.098	3	0.778	3.123	6	0.793
If the mother diagnosed with diabetes mellitus	1.649	3	0.638	14.791	6	0.022
If the mother had any other chronic illness	0.534	3	0.911	6.192	12	0.906
If the mother receive any medication during your last pregnancy	5.241	3	0.155	7.104	6	0.311
If the mother SCA diseased or carrier	2.241	3	0.430	-	-	-

influenced birth weight in the SCA group, while diabetes mellitus was correlated with gestational age in the control group. Managing these co-morbidities is essential for optimizing pregnancy outcomes. These results agreed with the other studies that showed evidence that pregnancy complications were substantially correlated with diabetes mellitus and hypertension, regardless of the diagnosis of pre-eclampsia in the affected mothers, and this supports the causal effects that link hypertension, body mass index and diabetes mellitus to reduced birth weight in mothers.[30,31]

Concerning gestational maturity, there is no significant difference between the SCA mothers and the control group; also, there is no significant correlation between the gestational maturity of the delivered babies and the mothers' variables. Our result is consistent with one study that concluded that after adjusting for other related risk factors for preterm delivery, women with sickle cell trait had an 85% lower risk of premature delivery at less than 32 weeks gestation. Interestingly, pregnancy plurality appeared to affect the decrease in preterm birth, with a more substantial impact in women with multiple pregnancies.[32]

Despite the significant presence of SCA in Saudi Arabia's southwestern region, this is the first investigation into how SCA affects newborn birth weight and gestational maturity, which can be considered a strength. However, this study's limitation arises from the case-control design, as there was still a chance of being affected by selection bias. In addition, data collection was challenged by the small sample size during the study period. Moreover, we could not examine every medical record in the database to corroborate further information about the participant mothers. Further research with a larger sample and more comprehensive medical record analysis would provide additional insights into the impact of SCA on pregnancy outcomes.

In conclusion, with the advancement in the management of SCA in pregnant mothers and newborns, including immunizations, newborn screening, and antibiotic prophylaxis beginning at birth, newborn survival rates and overall illness outcomes have significantly decreased, as well as maternal and neonatal mortality rates. However, compared to the general population, pregnancy with SCA is still linked to increased clinical and obstetric problems. This study indicates that SCA in pregnant mothers influences LBW. Additionally, the study spotlights the effect of other maternal factors and co-morbidities like maternal age and hypertension on pregnancy outcomes. Therefore, a multidisciplinary strategy must monitor these risky pregnancies well to sidestep avoided neonatal outcomes.

SCA in pregnant women can increase the risk of LBW in infants. Adequate antenatal care, management of maternal risk factors, and a multidisciplinary approach are necessary to minimize complications and ensure better outcomes for both mother and baby in SCA pregnancies.

REFERENCES

1. Tan TL, Khanapure A, Oteng-Ntim E. Sickle-cell trait and small-for-gestational age babies: is there a link? *J Obstet Gynaecol* 2008;**28**:298–300.
2. Boafor TK, Olayemi E, Galadanci N, Hayfron-Benjamin C, Dei-Adomakoh Y, Segbefia C, et al. Pregnancy outcomes in women with

sickle-cell disease in low and high-income countries: a systematic review and meta-analysis. *BJOG* 2016;**123**:691–8.
3. Maulik D. Fetal growth restriction: the etiology. *Clin Obstet Gynecol* 2006;**49**:228–35.
4. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. *Fetal Diagn Ther* 2014;**36**:117–28.
5. Smith-Whitley K. Complications in pregnant women with sickle cell disease. *Hematology Am Soc Hematol Educ Program* 2019;**2019**: 359–66.
6. Kingdom J, Huppertz B, Seaward G, Kaufmann P. Development of the placental villous tree and its consequences for fetal growth. *Eur J Obstet Gynecol Reprod Biol* 2000;**92**:35–43.
7. Villers MS, Jamison MG, De Castro LM, James AH. Morbidity associated with sickle cell disease in pregnancy. *Am J Obstet Gynecol* 2008;**199**:125.e1–5.
8. Jain D, Atmapoojya P, Colah R, Lodha P. Sickle cell disease and pregnancy. *Mediterr J Hematol Infect Dis* 2019;**11**:2019040.
9. Barfield WD, Barradas DT, Manning SE, Kotelchuck M, Shapiro-Mendoza CK. Sickle cell disease and pregnancy outcomes: women of African descent. *Am J Prev Med* 2010;**38**:S542–9.
10. Jastaniah W. Epidemiology of sickle cell disease in Saudi Arabia. *Ann Saudi Med* 2011;**31**:289–93.
11. AlHamdan NA, AlMazrou YY, AlSwaidi FM, Choudhry AJ. Premarital screening for thalassemia and sickle cell disease in Saudi Arabia. *Genet Med* 2007;**9**:372–7.
12. Alharbi SM, Alshaiti JH, Ghazwani JM, Ghazwani AM, Alshahrani NM, Banjar MY, et al. Epidemiology of hereditary anemias in Saudi Arabia. *Int J Community Med Public Health* 2021;**8**:6127–31.
13. ACOG Committee Opinion No 579: Definition of term pregnancy. *Obstet Gynecol* 2013;**122**:1139–40.
14. Population in Jazan region by gender, age group, and nationality (Saudi/Non-Saudi)/2019. Available at https://www.stats.gov.sa/en/6140 Accessed on December 21, 2022.
15. Preterm birth. World Health Organization fact sheets/2022 Available at https://www.who.int/news-room/fact-sheets/detail/preterm-birth. Accessed on December 21, 2022.
16. Damhuis SE, Ganzevoort W, Gordijn SJ. Abnormal fetal growth: small for gestational age, fetal growth restriction, large for gestational age: Definitions and epidemiology. *Obstet Gynecol Clin North Am* 2021;**48**:267–79.
17. Chiavaroli V, Derraik JG, Hofman PL, Cutfield WS. Born large for gestational age: bigger is not always better. *J Pediatr* 2016;**170**:307–11.
18. Thame M, Osmond C, Serjeant GR. Fetal growth in women with homozygous sickle cell disease: an observational study. *Eur J Obstet Gynecol Reprod Biol* 2013;**170**:62–6.
19. Ganesh B, Rajakumar T, Acharya SK, Kaur H. Sickle cell anemia/sickle cell disease and pregnancy outcomes among ethnic tribes in India: an integrative mini-review. *J Matern Fetal Neonatal Med* 2022;**35**:4897–904.
20. Galiba Atipo Tsiba FO, Itoua C, Ehourossika C, Ngakegni NY, Buambo G, Potokoue Mpia NS, et al. Pregnancy outcomes among patients with sickle cell disease in Brazzaville. *Anemia* 2020;**2020**:1989134.
21. 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.
22. Brown S, Merkow A, Wiener M, Khajezadeh J. Low birth weight in babies born to mothers with sickle cell trait. *JAMA* 1972;**221**:1404–5.
23. Roopnarinesingh S, Ramsewak S. Decreased birth weight and femur length in fetuses of patients with the sickle-cell trait. *Obstet Gynecol* 1986;**68**:46–8.
24. Decastel M, Leborgne-Samuel Y, Alexandre L, Merault G, Berchel C. Morphological features of the human umbilical vein in normal, sickle cell trait, and sickle cell disease pregnancies. *Hum Pathol* 1999;**30**:13–20.
25. Trampont P, Roudier M, Andrea AM, Nomal N, Mignot TM, Leborgne-Samuel Y, et al. The placental-umbilical unit in sickle cell disease pregnancy: a model for studying in vivo functional adjustments to hypoxia in humans. *Hum Pathol* 2004;**35**:1353–9.
26. Koshy M. Sickle cell disease and pregnancy. *Blood Rev* 1995;**9**:157–64.
27. Hassell K. Pregnancy and sickle cell disease. *Hematol Oncol Clin North Am* 2005;**19**:903–16, vii.
28. Jain D, Atmapoojya P, Colah R, Lodha P. Sickle cell disease and pregnancy. *Mediterr J Hematol Infect Dis* 2019;**11**:e2019040.
29. Afolabi BB, Babah OA, Adeyemo TA, Odukoya OO, Ezeaka CV, Obinyo Nwaiwu O, et al. Low-dose aspirin for preventing intrauterine growth restriction and pre-eclampsia in sickle cell pregnancy (PIPSICKLE): a randomized controlled trial (study protocol). *BMJ Open* 2021;**11**:e047949.
30. Ardissino M, Slob EA, Millar O, Reddy RK, Lazzari L, Patel KH, et al. Maternal hypertension increases risk of preeclampsia and low fetal birthweight: genetic evidence from a Mendelian randomization study. *Hypertension* 2022;**79**:588–98.
31. Ye W, Luo C, Huang J, Li C, Liu Z, Liu F. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2022;**377**:e067946.
32. Bryant AS, Cheng YW, Lyell DJ, Laros RK, Caughey AB. Presence of the sickle cell trait and preterm delivery in African-American women. *Obstet Gynecol* 2007;**109**:870–4.