Placenta and Reproductive Medicine

ORIGINAL ARTICLE

A retrospective study of pregnancy outcomes when intravenous immunoglobulin is used for the treatment of recurrent spontaneous miscarriages with subchorionic hematoma

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Abstract

Objective: To investigate the incidence of subchorionic hematoma (SCH), pregnancy outcomes and health status of offspring in patients with recurrent spontaneous miscarriage (RSA) treated with intravenous immunoglobulin (IVIg). **Methods:** The records of 775 patients with RSA were retrospectively reviewed. RSA with SCH were all treated with IVIg. Pregnancy outcomes examined were the rates of miscarriage, stillbirth, pre-term birth, and live birth. The pregnancy complications and comorbidities examined included oligohydramnios, hypertensive disorders, gestational diabetes, premature membrane rupture, placental adhesions, placenta previa, postpartum hemorrhage, placental abruption, and low birth weight. The health status of offspring of RSA patients with SCH was followed up by telephone, record physical and neurodevelopmental performance, and diseases under 5 years old, then compare with common children. Based on the ratio of SCH volume to that of the gestational sac, SCH was divided into small (ratio < 20%), moderate (ratio = 20%–50%), and large (ratio > 50%). Statistical analysis was performed with IBM SPSS Statistics 23.0. Comparison of continuous variables was analyzed using *t*-test. Categorical variables were compared by using χ^2 test or Fisher's exact test. Multivariable logistic regression was used for adjusting certain confounders. **Results:** Of the 775 patients with RSA, 110 RSA had a SCH (incidence = 14.2%). SCH was firstly found at 8.29 (5.00–11.58) weeks pregnant. There was no statistical difference in age, number of pregnancies, parity and miscarriages between patients with and without an SCH. The incidence of SCH in *in-vitro* fertilization embryo transfer (IVF-ET) patients was higher than in natural pregnancy patients (27.9% *vs*. 13.1%, $P < 0.05$). RSA with SCH patients with pregnancy outcome data called Group A ($n = 94$), RSA without SCH patients with pregnancy outcome data called Group B ($n = 556$), the rates of miscarriage (17.0% *vs*.12.4%), stillbirth (0 *vs.* 0.4%), pre-term delivery (9.6% *vs*. 10.8%), live birth (84.7% *vs.* 80.9%), and pregnancy complications were not different between Group A and B. The rate of vaginal bleeding in the Group A was higher than in the Group B ($P < 0.05$). There was no significant difference in the birth weight, the rate of low birth weight infants, neonatal asphyxia, or neonatal pneumonia between the groups. 43 puerpera in the experimental group were willing to receive telephone follow-up, who gave birth from December 2015 to November 2016. A total of 43 live births were delivered. By March 2022, the children were 5 years and 4 months old to 6 years and 3 months old. There is no difference in the physical development compared with common children. A child was diagnosed with neuropsychological delay. The incidence rate of community acquired pneumonia (CAP) was 27.9 per 1000 person-years for children under 5 years. In patients with a SCH and vaginal bleeding, the rate of preterm birth was

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Peer review under responsibility of Scholar Media Publishing.

Citation:
Zhu L, Huang Y, Li F, Ji X, Liu Y, Fu S, *et al*. A retrospective study of pregnancy outcomes when intravenous immunoglobulin is used for the treatment of recurrent spontaneous miscarriages with subchorionic hematoma. Placenta Reprod Med 2022;1:9.

DOI: 10.54844/prm.2022.0099

Received: 17 May 2022
Accepted: 07 September 2022
Published: 30 December 2022

16.7%. The rate of preterm birth was highest (36.4%) in RSA patients with a large SCH, and only 5.7% in patients with a small SCH ($P < 0.05$). Patients treated with IVIg had mild adverse reactions such as hypothermia, dizziness, and rash with rates of 1.8%, 1.8%, and 0.9%, respectively. **Conclusion:** The incidence of SCH was 14.2% in RSA. Pregnancy outcomes were similar between the RSA patients with a SCH treated with IVIg treatment and RSA patients without a SCH. There is no difference in the physical development between offspring of RSA with SCH and common children, and effect of SCH on neurodevelopment of offspring needs to be further verified by expanding the sample size. RSA patient with a SCH are prone to have vaginal bleeding and abdominal pain. For RSA patients with a SCH and vaginal bleeding, or SCH volume ratio > 50%, even after IVIg, still leads to a significantly higher preterm birth rate.

Key words: recurrent miscarriage, subchorionic hematoma, pregnancy outcome, offspring health

INTRODUCTION

The American Society of Reproductive Medicine defines recurrent spontaneous miscarriage (RSA) as 2 or more fetal loses.[1] The incidence of RSA ranges from 1% to 5%.[2] Patients with RSAs may develop damage to the endometrium which can lead to complications such as intrauterine adhesions, infection, and infertility. In addition, RSAs can have adverse psychological effects on women and their families. The risks of miscarriage, premature delivery, and gestational hypertension are higher in women with RSAs than those without. In addition, the incidence of subchorionic hematoma (SCH) is higher in patients with a history of RSAs.[3] However, the underlying mechanisms of SCH occurrence in patients with RSAs are unknown.

Subchorionic hematoma refers to the separation of chorionic villi and decidua during pregnancy, with blood accumulating between the chorion and the sacral membrane to form a hematoma. Because the lower edge of the hematoma often connects with the mouth of uterus, most patients have vaginal bleeding, and the diagnosis is made with ultrasound examination. The incidence of SCH varies with the population studied, and ranges between 0.46% and 22.00%.[4,5] A meta-analysis showed that the occurrence of SCH is closely related to premature delivery, spontaneous miscarriage, placental abruption, and premature rupture of membranes.[6] For example, the preterm birth rate of women with a normal pregnancy was 8.9%, but was 17.6% in patients with a SCH. A prospective study by Sandor *et al.*[7] compared pregnancy outcomes in 187 patients with a SCH and 6488 patients without, and found that patients with a SCH had a significantly higher risk of adverse pregnancy outcomes and pregnancy complications such as gestational hypertension, placental abruption, premature delivery, fetal growth restriction, and intrauterine distress.

Most of the research on SCH is focused on normal pregnant women, or pregnant women with a history of infertility. Few studies have examined patients with RSAs complicated by a SCH. The purpose of this study was to examine the incidence of SCH in RSA patients, and pregnancy outcomes and health status of offspring after intravenous immunoglobulin (IVIg) treatment.

MATERIALS AND METHODS

Study subjects

The records of pregnant patients with a history of RSA seen at Sun Yat-sen Memorial Hospital of Sun Yat-sen University from May 2015 to April 2016 were retrospectively reviewed. Exclusion criteria for the study were incomplete administration information, unidentified pregnancy location, biochemical pregnancy, ectopic pregnancy, and multiple pregnancies. In total, 775 patients with a history of RSAs and a single intrauterine pregnancy were included in the analysis. The study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (Approval No. 2013 [04]). All included patients gave their oral and written informed consent.

Research methods

Data extracted from the medical records included age, number of pregnancies, parity, number of previous miscarriages, way of conception, and the presence of vaginal bleeding and abdominal pain. Pregnancy outcomes examined were spontaneous miscarriage, stillbirth (fetal death), preterm/full-term vaginal delivery, preterm/full-term cesarean delivery, and induction delivery. Pregnancy complications and comorbidities examined were oligohydramnios, hypertensive disorders of pregnancy, gestational diabetes mellitus/pregnancy complicated with diabetes, preterm premature rupture of membranes, placental adhesions/placenta accreta, postpartum hemorrhage, placental abruption, placenta previa, and low birth weight.

The health status of offspring of RSA patients with SCH was followed up by telephone, to know development and diseases under 6 years. Physical development examined were the time of fontanelle closure, time of deciduous tooth eruption, height and weight, and draw the growth curve of height and weight aged 0–6 years. The motor and neurodevelopmental performance was assessed by gross motor, fine motor, language, social adaptation, psychology and emotion. And then compare health status of offspring with common children.

During the study period, RSA patients with a SCH at early

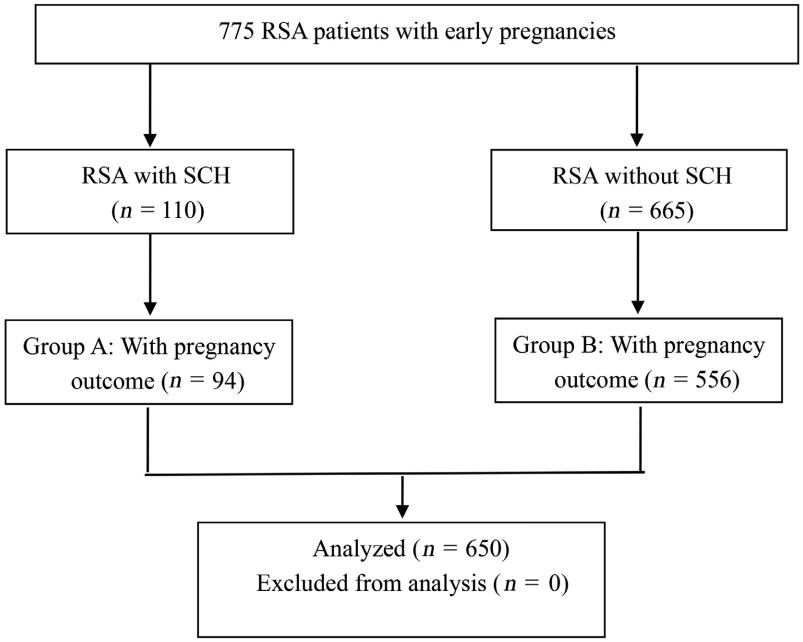

Figure 1. Analysis flow chart. RSA: recurrent spontaneous miscarriage; SCH: subchorionic hematoma.

gestation were treated with IVIg. The treatment protocol was intravenous administration of human globulin, 25 grams, over 8 hours. One administration was performed per day for a total of 3 days. RSA patients with a SCH at early gestation with pregnancy outcome data were assigned to the Group A, while RSA patients without a SCH and pregnancy outcome data were assigned to the Group B.

Statistics analysis

Statistical analysis was performed with SPSS Statistics 23.0 (IBM, Chicago, USA). Mean ± Standard Deviation (SD) with range or median ± quartile were used for the continuous data. Absolute numbers or percentage were used for reporting the categorical data. Comparison of continuous variables was analyzed using *t*-test. Categorical variables were compared by using χ^2 test or Fisher's exact test. Multivariable logistic regression was used for adjusting certain confounders. Pair-wise comparisons were conducted with the Bonferroni method. A value of $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Demographic data

Of the 775 RSA patients, 110 patients had a SCH and 665 patients did not (Figure 1). The incidence of SCH was 14.2%. SCH was discovered for the first time at 8.29 (5.00–11.58) weeks pregnant. There were no significant differences in age, number of pregnancies, parity, and number of miscarriages between the 2 groups, and conception method had statistical differences (Table 1). 93 patients had a SCH in 708 natural pregnancy patients (13.1%), 17 patients had a SCH in 61 *in-vitro* fertilization embryo transfer (IVF-ET) patients (27.9%), artificial insemination patients had no SCH. There was statistical difference in the incidence of SCH between natural pregnancy and IVF-ET patients ($P < 0.05$). The results of multiple logistic regression equation showed that methods of conception had statistical significance for the formation of SCH (OR = 1.47, 95% CI 1.06–2.05, $P = 0.022$). ART was a high risk for the SCH (Table 2).

Pregnancy outcomes

Of the patients, 94 in RSA with SCH (Group A) and 556 in RSA without SCH (Group B) had pregnancy outcomes (Figure 1). There were no significant differences in the rate of shedding ($P = 0.626$), miscarriage, stillbirth, and preterm birth between the 2 groups. The live birth rate was 80.9% (76/94) in the Group A, and 84.7% (471/556) in the Group B ($P = 0.343$). The average gestational age was 38.3 weeks in the Group A and 38.4 weeks in the Group B ($P = 0.505$) (Table 3).

Pregnancy comorbidities and complications

There were 76 live births in the Group A and 471 live births in the Group B. The rates of pregnancy comorbidities and complications including oligohydramnios, gestational hypertensive disorder, and gestational diabetes, premature rupture of membranes, placental abruption, placental adhesions/placental implantation, postpartum hemorrhage, and placenta previa were not different between the 2 groups (Table 4).

Threatened miscarriage symptoms

The incidence of vaginal bleeding was significantly higher in the Group A ($P = 0.024$). The incidence of abdominal pain was similar in both groups (Table 5).

Analysis of threatened miscarriage symptoms and pregnancy outcome in RSA patients with SCH

In the Group A, patients with vaginal bleeding had a higher preterm birth rate (16.7%) than those without vaginal bleeding ($P = 0.042$). There was no significant difference in the preterm birth rate between those with abdominal pain and those without (Table 6).

Comparison of neonatal outcomes

There were 76 neonates in the Group A and 471 in the Group B. The average birth weight of the newborns was 3.07 kg in the Group A and 3.09 kg in the Group B ($P = 0.761$).

There were no significant differences of newborn weight (3.07 kg *vs.* 3.09 kg), or the rate of pediatric pneumonia, low birth weight infants, neonatal asphyxia, neonatal

Table 1: Comparison of demographic data

Demographic data	RSA with SCH (*n* = 110)	RSA without SCH (*n* = 665)	*P*-Value
Age, y	31.34 ± 3.75	31.18 ± 4.21	0.546
Pregnancies, *n*	4.00 (3.00–5.00)	4.00 (2.00–6.00)	0.323
Births, *n*	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.345
Miscarriages, *n*	2.00 (2.00–3.00)	2.00 (1.00–3.00)	0.833
Early miscarriages	2.00 (0.00–4.00)	2.00 (1.00–3.00)	0.146
Late miscarriages	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.372
Conception method, *n* (%)			0.011*
Natural pregnancy	93 (84.5)	615 (92.5)	
Artificial insemination	0	6 (0.9)	
IVF-ET	17 (15.5)	44 (6.6)	

*$P < 0.05$. RSA: recurrent spontaneous miscarriage; SCH: subchorionic hematoma; IVF-ET: *in-vitro* fertilization embryo transfer.

Table 2: Multiple logistic regression analysis

Demographic data	*P*-Value	OR	OR [95% CI]
Age	0.685	1.01	0.96–1.07
Number of pregnancies	0.191	0.81	0.60–1.11
Number of births	0.878	0.95	0.50–1.80
Number of abortions	0.271	1.27	0.83–1.95
Number of early abortions	0.318	0.86	0.65–1.15
Number of late abortions	0.734	0.92	0.57–1.49
Conception method[#]	0.022*	1.47	1.06–2.05

[#]Compare with Natural pregnancy. *$P < 0.05$.

Table 3: Comparison of pregnancy outcomes (*n* [%])

Pregnancy outcomes	Group A (*n* = 94)	Group B (*n* = 556)	*P*-Value
Natural miscarriage	16 (17.0)	69 (12.4)	0.220
Early miscarriage (< 12 weeks)	12 (12.8)	54 (9.7)	0.365
Late miscarriage (≥ 12 weeks)	4 (4.2)	15 (2.7)	0.618
Stillbirth	0	2 (0.4)	0.731
Induction of labor	2 (2.1)	11 (2.0)	1.000
Fetal malformation induced labor	1 (1.1)	10 (1.8)	0.937
Other factors resulting in pregnancy termination	0	3 (0.5)	1.000
Live birth	76 (80.9)	471 (84.7)	0.343
Pre-term birth	9 (9.6)	60 (10.8)	0.723
Full-term birth	67 (71.3)	411 (73.9)	0.591

Table 4: Comparison of pregnancy comorbidities and complications (*n* [%])

Comorbidities and complications	Live births in Group A (*n* = 76)	Live births in Group B (*n* = 71)	*P*-Value
Oligohydramnios	2 (2.6)	38 (8.1)	0.091
Gestational hypertensive disorder	1 (1.3)	20 (4.2)	0.337
Gestational diabetes	16 (21.1)	110 (23.4)	0.658
Premature membrane rupture	4 (5.3)	32 (6.8)	0.358
Placental abruption	0	5 (1.1)	0.596
Placental adhesions	10 (13.2)	33 (7.0)	0.225
Postpartum hemorrhage	5 (6.6)	13 (2.8)	0.333
Placenta previa	2 (2.6)	11 (2.3)	1.000

Table 5: Threatened miscarriage symptoms (*n* [%])

Threatened miscarriage symptoms	Group A (*n* = 94)	Group B (*n* = 556)	*P*-Value
Vaginal bleeding	48 (51.1)	215 (38.7)	0.024*
Abdominal pain	20 (21.3)	80 (14.4)	0.087

*$P < 0.05$.

Table 6: Associations of vaginal bleeding and abdominal pain and pregnancy outcomes in the Group A (*n* [%])

Pregnancy outcomes	Vaginal bleeding		*P*-Value	Abdominal pain		*P*-Value
	Yes (*n* = 48)	No (*n* = 46)		Yes (*n* = 20)	No (*n* = 74)	
Spontaneous miscarriage	10 (20.8)	6 (13.0)	0.315	4 (20.0)	12(16.2)	0.949
Pre-term birth	8 (16.7)	1 (2.2)	0.042*	3 (15.0)	6 (8.1)	0.616
Full-term birth	29 (60.4)	38(82.6)	0.017*	13(65.0)	54(73.0)	0.484
Stillbirth	0	0	--	0	0	--
Other	1 (2.1)	1 (2.2)	1.000	0	0	--

*$P < 0.05$.

Table 7: Comparison of neonatal outcomes

Neonatal outcomes	Group A (*n* = 76)	Group B (*n* = 471)	*P*-Value
Average birth weight, kg	3.07 ± 0.12	3.09 ± 0.29	0.761
Number of low birth weight infants, *n*(%)	9 (11.8)	45 (9.6)	0.535
Neonatal asphyxia, *n*(%)	2 (2.6)	18 (3.8)	0.854
Neonatal pneumonia, *n*(%)	4 (5.3)	7 (1.5)	0.083
Pediatric referrals, *n*(%)	23 (30.3)	124 (26.3)	0.473

Table 8: Comparison of effects of hematoma size on pregnancy outcomes (*n* [%])

Pregnancy outcomes	Small (*n* = 53)	Medium (*n* = 6)	Large (*n* = 11)	*P*-Value
Natural miscarriage	6 (11.3)	1 (16.7)	3 (27.3)	0.283
Stillbirth	0	0	0	--
Premature birth	3^{a} (5.7)	$0^{a, b}$	4^{b} (36.4)	0.024*
Full-term birth	44^{a} (83.0)	$5^{a, b}$ (83.3)	3^{b} (27.3)	0.001*
Live birth	47 (88.7)	5 (83.3)	7 (63.6)	0.084
Induced labor	0	0	1 (9.1)	0.243

^{a,b}: the subsets of the variable, and at the 0.05 level, there is not significant difference among groups. *$P < 0.05$.

pneumonia, and pediatric referrals between the 2 groups (Table 7).

43 puerpera in the Group A were willing to receive telephone follow-up, who gave birth from December 2015 to November 2016. By March 2022, the children were 5 years and 4 months old to 6 years and 3 months old. There is no difference in the time of fontanelle closure and deciduous tooth eruption between 43 children and common children. Most of their growth curve were within the normal range, 65.1% of children' height and weight for age were in the range of X ± SD, and 97.7% were in the range of X ± 2SD. 42 children's gross motor, fine motor, language development, social adaptation, psychology and emotion were similar with, and a child was diagnosed with neuropsychological delay. For children under 5 years, the incidence rate of community acquired pneumonia (CAP) was 27.9 per 1000 person-years. 1 case of immune thrombocytopenia, 1 case of congenital pyloric obstruction, 2 cases of indirect inguinal hernia, 1 case of testicular hydrocele surgery, 5 cases of allergic constitution, 1 case of vitiligo, 1 case of adenoid hypertrophy.

Relation between hematoma size and pregnancy outcomes

Based on ultrasound scanning, the ratio of the volume of the SCH to that of the gestation sac was calculated with the following formula[8]:

$$\frac{\text{SCH length} \times \text{width} \times \text{height} \times 0.52}{\text{Gestational sac length} \times \text{width} \times \text{height} \times 0.52}$$

The size of the SCH was then classified as small (ratio < 20%), medium (ratio = 20%–50%), and large (ratio > 50%, Figure 2). For RSA patients with a large SCH, the spontaneous miscarriage rate was 27.3%, the premature birth rate was 36.4%, and the live birth rate was 63.6% (Table 8).

Adverse drug reactions

RSA patients occasionally had mild adverse reactions to IVIg treatment. These included hypothermia, dizziness, and rash, with rates of 1.8%, 1.8%, and 0.9%, respectively. The symptoms resolved 1–2 days after treatment was completed. No serious adverse reactions such as laryngeal edema occurred.

DISCUSSION

The incidence of SCH in normal pregnant women ranges from 1.3% to 3.1%.[7,9] This study found that the incidence of SCH in RSA patients was 14.2%, much higher than that in a normal population. Tower *et al.*[3] reported the incidence of SCH in RSA patients was 12%. The etiology of SCH is not known. Laxmi *et al.*[10] analyzed 5 patients with SCH and suggested that the occurrence of SCH is associated with thrombosis and vasculitis resulting from autoantibodies. The increased incidence of SCH in RSA patients may be related to abnormal autoimmune function. However, this study examined peripheral antiphospholipid antibody levels, and none of those examined were increased in RSA patients with SCH. The relation of other autoantibodies, such as antinuclear antibody, to the occurrence of SCH should be examined in future studies.

Some researchers believe SCH may be due to dominant Th1 cytokines.[11] In patients with threatened miscarriage symptoms and SCH in early gestation, the concentration of serum Th1 cytokine γ-interferon was significantly higher than that in normal pregnant women.[11–13] γ-Interferon can activate the decidual vascular endothelial cells to release prothrombinase, which converts prothrombin into the active thrombin. The thrombin stimulates endothelial cells to secret interleukin (IL)-8 and recruits polymorphonuclear (PMN) leukocytes, which can destroy decidual endothelial cells and damage the decidual vessels. In addition, a high level of γ-interferon is closely related high levels of natural killer (NK) cells, which can kill decidual endothelial cells without pre-sensitization, and involve specific antibodies.[14] It has been considered that the use of aspirin and low-molecular-weight heparin to treat anti-phospholipid syndrome in RSA patients may be related to the occurrence of SCH.[15] Truong *et al.*[16] reported the use of aspirin instead of low-molecular-weight heparin increased the incidence of SCH in the RSA patients and patients with infertility. However, the study did not analyze pregnancy outcomes. Zhou *et al.*[17] showed the incidence of SCH in patients undergoing IVF-ET was about 12.1%, and that fresh embryo transfer was more

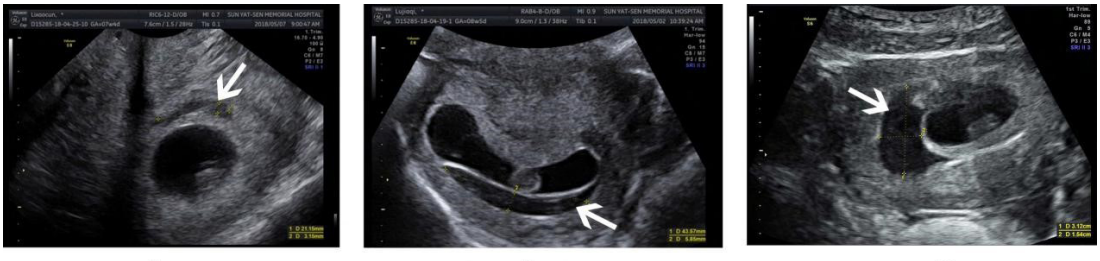

Figure 2. SCH under ultrasound. (A) Small SCH; (B) Medium SCH; (C) Large SCH. Arrow means SCH. SCH: subchorionic hematoma.

likely to cause SCH. The birth weight of infants of SCH patients was lower. In our research, the incidence of SCH in IVF-ET patients was higher than in natural pregnancy patients (27.9% *vs.* 13.1%, $P < 0.05$), which suggested that IVF-ET may be a risk factor for SCH.

The presence of SCH in early gestation may be associated with an increased rate of adverse pregnancy outcomes. In 1990 Pedersen *et al.*[18] followed-up 23 SCH patients in mid-term pregnancy. The occurrence of SCH was at 12 to 20 weeks' gestation. The average SCH volume was 71 ml. The miscarriage rate was 4.3%, and the preterm birth rate was 8.6%. These data suggested that SCH occurring in mid-term pregnancy did not increase the incidence of adverse pregnancy outcomes. In 1998 a study showed that patients with SCH occurring in early gestation had a higher rate of spontaneous miscarriage and preterm birth (77%) if the SCH persisted throughout pregnancy and caused vaginal bleeding.[5] In 2015 Palatnik *et al.*[19] compared 512 patients with SCH occurring in early gestation and 1024 normal pregnant women. They found that SCH patients had a shorter cervix than the normal patients at 18–22 weeks' gestation, and a preterm birth rate of 12.5%. Our study showed that after IVIg treatment, RSA patients with SCH in early gestation (5.00–11.58 weeks) had a similar rate of adverse pregnancy outcomes (preterm birth rate = 9.6%) and pregnancy complications as Group B. The results suggested that IVIg treatment can improve pregnancy outcomes in these patients. Moreover, patients with a large SCH (volume ratio > 50%) had a high preterm birth rate (36.4%) after IVIg therapy, and thus deserve closer monitoring.

The mechanism by which IVIg treatment improves pregnancy outcomes in patients with a SCH may be related to immunomodulation. Immunoglobulins may promote the production of Th2 cytokines, thereby facilitating embryo implantation and pregnancy.[20] The IgG represents 90% of human immunoglobulin, and has intact Fa and Fc segments. The antigen CD 16 on the surface of NK cells is a receptor of the Fc segment. Intravenous perfusion of the Fc segment may partially inhibit the toxic effects of NK cells by binding to CD 16 on their surface.[21]

The present study also analyzed the neonatal outcomes of RSA patient with a SCH and those without. The results showed that the weight of the newborns was similar between the 2 groups. The incidence of low-birth-weight infants, neonatal asphyxia, neonatal pneumonia, and pediatric department transfers were also similar between the groups. In addition, the physical development of children aged 0–6 in the Group A was not significantly different from normal population, but a child conceived naturally was diagnosed with neuropsychological delay by a pediatrician, and he is currently undergoing behavioral intervention. A research included 56 cases of vascular placental pathologies detected by magnetic resonance imaging (such as SCH) reports are associated with high neurological impairment.[22] Currently there is not enough evidence that confirm the damage of SCH on offspring growth and development. For children under 5 years, the incidence of CAP was 27.9 per 1000 person-years in our study, which was lower than 65.8 in Chinese urban children of the same age.[23]

The RSA patients with a SCH had a higher rate of vaginal bleeding, which resulted in a higher preterm birth rate. This result is consistent with a study by Sharma *et al.*[24] Sukur *et al.*[25] confirmed that patients with symptoms of a threatened miscarriage and a SCH before 20 weeks' gestation had a higher risk of spontaneous miscarriage. This is probably because vaginal bleeding may cause vaginal pathogens to grow and subsequently an ascending infection and inflammation. IVIg treatment reduce preterm labor may be related to immunomodulation and anti-inflammation. Therefore, the preterm birth rate of RSA with SCH after IVIg treatment was not significantly different from that of the general RSA population in our study.

The size of the SCH plays an important role in pregnancy outcomes. In 1996 a study[26] reported that a large SCH separation was found to be associated with an almost threefold increase in risk of spontaneous abortion. Dongol *et al.*[27] conducted a prospective study of 70 patients with threatened miscarriage symptoms, and found that 43% of the patients had a SCH, and that a size ≥ 20 cm^2 may increase the risk of spontaneous miscarriage. And it was associated with an increased risk of preterm birth, which is consistent with a study by Al *et al.*[28]

There is no consensus on effective treatments for SCH. Some studies[29,30] used fat emulsion combined with vaginal progesterone to treat SCH, and found the treatment alleviated symptoms of a threatened miscarriage. However, few studies examined the effects of the treatment on pregnancy outcomes, and complications and comorbidities during pregnancy. Another study[12] used oral dydrogesterone to treat SCH, and showed a benefit in reducing the miscarriage rate. However, effects on the premature birth and premature membrane rupture rates were not examined.

The present study confirmed that RSA patients had a higher incidence of SCH, and that immunoglobulin treatment improved pregnancy outcomes. However, the presence of vaginal bleeding, even after immunoglobulin treatment, still leads to a significantly higher preterm birth rate. RSA patients with a SCH volume ratio > 50% had the highest preterm birth rate, while smaller SCH volume ratios were not related to a marked increase in the preterm birth rate.

However, our research still has limitation. We did not set an SCH without IVIg group, because our research subjects are patients who suffer from recurrent abortion. These patients are suffering both physically and mentally. Moreover, many

previous studies reported that the incidence of adverse pregnancy outcomes can be increased by SCH, so the vast majority of patients are not willing to serve as the control group. We hope that in the follow-up study, we will expand the scope of the study population, carry out randomized controlled studies, and deeply study the therapeutic effect of IVIg on SCH.

In conclusion, RSA patients with a SCH and vaginal bleeding, and RSA patients with a large SCH need to be strictly monitored to prevent preterm birth. The present study is a retrospective analysis, and thus may have selection bias and recall bias. Further prospective studies are needed to provide more information.

Source of Funding

This study was supported by the National Key Research and Development Program of China (2019YFA0801403), National Nature Science Foundation of China (81771660 and 81741017), the Guangdong Natural Science Foundation (2018A030313023, 2018A030313162, 2018A030310162, 18zxxt56 and 2021A1515110330), the Technology Innovation Strategy Fund of Guangdong Province (2018A030313737), the 5010 projects at Sun Yat-sen University (2012006), and the Science and Technology Planning Project of Guangdong Province (pdjh2020b0010) and Guangdong Basic and Applied Basic Research Foundation (2021B1515140035).

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (Approval No. 2013 [04]). All included patients gave their oral and written informed consent.

Conflict of Interest

Hui Chen is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member and her research group.

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