Preconception Care of Patients with Recurrent Spontaneous Abortion

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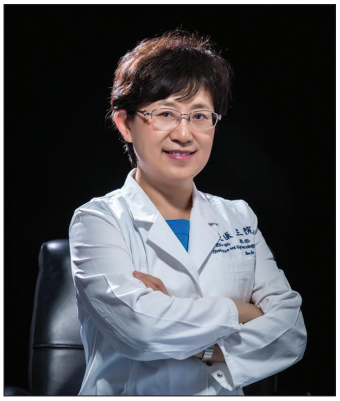

Prof. Jie Qiao, an academician of the Chinese Academy of Engineering, the president of Peking University Third Hospital, the third-term chairman for the Chinese Society of Reproductive Medicine of the Chinese Medical Association, and the chairman for the first session of the Society of Reproductive Medicine Professional Committee of the Chinese Medical Doctor Association, has dedicated herself to clinical and basic research in the field of obstetrics, gynecology, and reproductive medicine for nearly three decades. She has led her team to improve female fertility and provide novel approaches to prevent genetic birth defects. She has accomplished enormous work regarding obstetric, gynecological, and reproductive diseases from pathogenesis, diagnosis, and treatment to prognosis. The number of patients with complicated infertility treated by her team at Peking University Third Hospital under her guidance has amounted to more than 600,000 annually.

The incidence of recurrent spontaneous abortion (RSA) in women of reproductive age is 1%–5%, which is a heavy physical and emotional blow to these women. Repeated curettage of uterine cavity will damage the endometrium, causing partial infection and leading to intrauterine adhesion (IUA). Repeated pregnancy loss causes a huge emotional trauma to both the patients and their families, including negative emotions, such as anxiety, stress, and frustrations. Therefore, patients with RSA are eager to seek medical help from their doctors before pregnancy again. However, the causes of RSA are complicated, with 50% of cases having unexplained etiologies. Multiple controversies exist regarding the clinical treatments of RSA; hence, the preconception care about RSA is tough. Therefore, substantial attention should be given to the preconception care for women with RSA, which is very important for promoting successful pregnancy rates and preventing pregnancy complications. This article focuses on the subjects of preconception care, etiological screening, and preconception care in those women with RSA.

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Subjects of Preconception Care

The definition of RSA differs among countries. The controversy is mainly on the frequency of spontaneous abortion (SA) and gestational weeks, whether the SA is continuous or not, and whether biochemical pregnancy (BP) is SA or not.

As defined by the Practice Committee of American Society for Reproductive Medicine in 2012, recurrent pregnancy loss is a clinical pregnancy with two or more failed pregnancies, clearly excludes BP, and is without emphasis on continuous SA.[1] In 2016, the Society of Obstetrics and Gynecology of Chinese Medical Association also released *The Expert Consensus on the Diagnosis and Treatment of RSA*, in which RSA is defined as three or more consecutive miscarriages before the 28th gestational week. It is also suggested that the occurrence of two consecutive miscarriages should be considered and evaluated.[2] In 2017, as shown in the guideline of the German Society of Gynecology and Obstetrics, the Austrian Society of Gynecology and Obstetrics, and the Swiss Society of Gynecology and Obstetrics, RSA is defined as three or more consecutive miscarriages before the 20th gestational week. The definition emphasized the continuity of SA.[3] The gestational duration in RSA is defined by each country on the basis of its definition of the perinatal period.

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The overall incidence of SA in women of reproductive age is approximately 15%. As shown in previous studies, among women aged 25–29 years without a miscarriage history, nulliparous women had a miscarriage rate of 8.9% and parous women had a rate of 9.3%; among women with a history of one miscarriage, nulliparous women had a miscarriage rate of 12.4% and parous patients had a rate of 11.8%; for women with a history of two miscarriages, the rates are 22.7% and 17.7%, respectively; and for women with three or more abortions, the proportion of pregnancies ending in miscarriage increased to 44.6% in nulliparous women and to 35.4% in parous women. While the study did not emphasize whether the previous miscarriages were continuous or not,[4] it showed that the miscarriage rate in women with a history of one miscarriage was not significantly higher than that in women without a history of miscarriage; however, it increased markedly by approximately 20% in women with a history of two miscarriages and increased up to 40% in women with a history of three or more miscarriages. Therefore, most experts believe that preconception care is necessary for patients with two or more SAs.

As stated in the definition of RSA by the Practice Committee of American Society for Reproductive Medicine, clinical pregnancy is defined as a pregnancy confirmed by ultrasonography or histopathological examination, excluding BP, which refers to a condition in which human chorionic gonadotropin (hCG) from the embryo is detectable in maternal urine or blood, but the loss of the embryo before the existence of a gestational sac on ultrasonography ranges from 8% to 33% of total pregnancies. The etiology of BP is not clear and is likely caused by many factors such as absorbed ectopic gestation, uterine receptivity, chromosomal abnormalities of the embryo, poor-quality embryos, maternal hormone levels, and autoimmune diseases. Recurrent BP (RBP) is defined as two or more consecutive BPs. Research has shown that in RSA patients, the live birth rate in RBP is 41.7%, and is markedly lower than that of women who had one or no BP (72.9%).[5] Therefore, attention should be paid to RBP.

Etiological Screening and Preconception Care

The causes of RSA are complex, with several identified factors such as anatomical factors, genetic factors, endocrine factors, infectious disorders, thrombophilia, autoimmunity diseases, and unhealthy lifestyle. In addition, there are still about 50% of RSA patients having uncertain causes; even in patients with identified causes, pathogenesis and treatment strategies are controversial.

Anatomical factors

The incidence of genital anomalies in patients with RSA is about 19%,[6] which is higher than that of the general population. It includes congenital malformations, accounting for 7% of total cases, such as unicornuate uterus (0.7%), bicornuate uterus (0.8%), septate uterus (4.9%), and double uterus (0.2%), and acquired malformations, accounting for 12.9% of the total, such as IUA (4.1%), uterine fibroids (6.1%), and endometrial polyps (3.1%). However, not all genital malformations will lead to RSA, and correcting genital malformations may not necessarily reduce miscarriages.

In the case of anatomical uterine congenital anomalies, patients with septate uterus are at an increased risk of SA. As indicated in the retrospective cohort studies, hysteroscopic septum resection in women with septate uterus significantly lowered the incidence of SA and increased the live birth rate.[7] Because no randomized controlled trials were included, further studies are needed to determine whether a septate uterus requires surgery to reduce the miscarriage rate. The relationship between other types of anatomical anomalies and RSA is unclear. An analysis revealed that women with a bicornuate uterus had significantly increased rate of late miscarriages (14–24 weeks of gestation).[8] Other studies showed that surgery did not appear to lower the SA rate in patients with a bicornuate uterus.[9] The current sample of patients with unicornuate and bicornuate uterus is relatively small, and there is bias in retrospective studies, which is generally considered to be unrelated to RSA.

Controversies exist over whether acquired anatomical anomalies will increase the incidence rate of SA. It is generally acknowledged that IUA, uterine fibroids, and endometrial polyps could seriously affect the morphology and volume of the cavity, and the SA rate will be induced. Studies showed that a surgical procedure is required for patients with Asherman's syndrome, uterine fibroids, or endometrial polyps that protrude beyond the uterine cavity and have a diameter >1 cm.[10] In women of reproductive age with uterine fibroids but no symptoms, surgical treatment does not improve pregnancy outcomes.[11]

At present, it is recommended that RSA combined with septate uterus, IUAs, endometrial polyps, and uterine fibroids protruding in the uterine cavity and larger than 1 cm in diameter should be treated before pregnancy.

Couples with genetic anomalies

Chromosomal anomalies account for about 2%–5% of all RSA cases, including numerical and structural anomalies of chromosomes. Balanced translocations and Robertsonian translocations are the most common cases. (1) Balanced translocation carriers account for 0.2% of the population, namely, one carrier among 250 couples. During meiosis, translocated chromosomes and normal chromosomes could form 18 types of zygotes, among which only one normal genetic type and one translocation carrier type with normal phenotype are produced. The remaining 16 types are unbalanced gametes resulting in monosomy, partial monosomy, trisomy, and partial trisomy, which lead to miscarriages, fetal malformations, and fetal death. (2) Robertsonian translocation accounts for about 20.0% of RSA cases with chromosomal anomalies and are categorized into translocations between nonhomologous and homologous chromosomes. If carriers of nonhomologous Robertsonian translocations mate with persons with normal chromosomes, six different types of gametes are formed as a consequence of meiosis, namely one with normal chromosomes, one with Robertsonian translocation, and four with abnormal chromosomes. Individuals with homologous translocations could neither produce normal gametes nor give birth to offspring with normal karyotypes.

For RSA couples, G-banding karyotype analysis is widely used in prepregnancy screening for chromosomal abnormalities. Genetic counseling is recommended for couples with chromosomal abnormalities. During the process of *in vitro* fertilization-embryo transfer (IVF-ET), sperms and oocytes can form zygotes and develop into embryos *in vitro*. Based on IVF-ET, preimplantation genetic diagnosis (PGD) is conducted for genetic testing prior to embryo implantation into uterus so as to avoid genetic diseases. As for couples with RSA resulted from chromosomal abnormalities, PGD could reduce SA rate but make no significant difference in live birth rate. However, the prerequisite of PGD is the availability of high-quality blastula after IVF-ET, and normal-karyotyped blastula is not always available after genetic testing, which leads to the failure of the PGD cycle, similar to the process of SA at some level, and impose heavier economic burden to RSA families. For RSA couples with balanced translocations and Robertsonian translocations, PGD is recommended to mitigate secondary damage to uterus caused by recurrent miscarriages, which should be performed after thorough discussion with RSA couples and obtaining informed consent. Meanwhile, no objection is raised against natural pregnancy in RSA couples.

So far, there is no definite correlation between chromosomal polymorphism and RSA. A study showed that the incidence of chromosomal polymorphism in RSA couples (8.4%) was significantly higher than that of reproductively healthy population (4.9%). The most frequently observed polymorphism was "9qh+," but the sample size was limited to only 455.[12] Another study containing 4,599 samples demonstrated no statistically significant difference regarding chromosomal polymorphism between RSA group and reproductive healthy control group. Moreover, similar chromosomal polymorphisms were found in immediate relatives (including parents and siblings) of 38 couples with a history of adverse pregnancy; however, none of those relatives had adverse pregnancy history.[13] Therefore, RSA couples with chromosomal polymorphisms have not been considered as objects of preconception management so far.

Some studies showed that the occurrence of RSA was related to gene polymorphism. Genes involved in immune response (KIR2DS2, tumor necrosis factor [TNF], etc.), coagulation (F2, F5, etc.), angiogenesis (NOS3 and VEGFA), and metabolism (GSTT1 and MTHFR) were identified in RSA couples, but findings from different studies vary from each other. One meta-analysis in 2007 included 472 variants of 187 genes, but most of them were small-sample studies on one specific gene variant; thus, it did not reveal a clear relationship between single-gene polymorphism and RSA.[14]

Thalassemia is hereditary hemolytic anemia caused by abnormal hemoglobin production. It is an autosomal dominant hereditary disease. Intrauterine anemia may cause intrauterine fetal death which further develops into late-stage RSA. PGD could be applied to single out healthy embryos and reduce the risk of miscarriages.

Endocrine factors

Pregnancy maintenance requires support from hypothalamic–pituitary–ovary axis. Endocrine dysfunction will lead to RSA. About 8%–12% of RSA cases were caused by endocrine dysfunction, such as thyroid dysfunction, luteal phase defect (LPD), hyperprolactinemia (HPRL), polycystic ovary syndrome (PCOS), diabetes, and insulin resistance.

Thyroid hormone has irreplaceable effects on the body by promoting growth and metabolism. Fetus could not synthesize thyroid hormone within the first 12 weeks of gestation, and has to rely on the maternal supply. Thyroid dysfunction will lead to adverse pregnancy outcomes. Clinical hyperthyroidism and hypothyroidism will cause SA and require preconception treatments. Studies have shown that euthyroid women with a history of RSA had significantly higher rate of positive thyroid antibodies (thyroglobulin and thyroid peroxidase antibodies) than reproductively healthy women.[15] However, other studies came to different conclusions. Two meta-analyses in 2011 suggested that maternal thyroid antibodies are high-risk factors for RSA.[16,17] The mechanism is unclear, but some hypotheses have been proposed as follows: thyroid antibody induces autoimmune disorder and causes increased number of killing cytokines in the endometrium; it causes hypothyroidism during pregnancy; and it impedes the bio-effects of thyroid hormone by binding to hCG receptors on the surface of zona pellucida. For thyroid antibody-positive RSA patients, it is proposed that supplementation with thyroxine tablets or intravenous immunoglobulin (IVIg) could reduce SA risk, but there is no clear evidence to prove its validity and safety.[18] While for thyroid antibody-positive RSA patients with subclinical hypothyroidism, it is recommended to receive preconception treatment and monitor thyroid function after pregnancy.

The diagnosis of LPD is based on several detections, such as basal body temperature measurement, endometrial biopsy during luteal phase, and measurement of progesterone level after ovulation, which is difficult to be implemented clinically. Some experts recommended progesterone supplementation for RSA patients during pregnancy, but the effectiveness remains controversial. A multicentric, large-scale, randomized study in 2015 enrolled 1,568 RSA cases and found no statistically significant differences between the progesterone therapy group and control group.[19] Another meta-analysis conducted in 2017 indicated that progesterone supplementation could effectively reduce miscarriage rate, and is safe for both gravidas and fetuses.[20] For patients with LPD, ovulation of immature follicles should be prevented before pregnancy and progesterone therapy should be applied afterward.

About 40% of PCOS patients suffer from SA,[21] which might be associated with high level of androgen and luteinizing hormone (LH), poor endometrial receptivity, insulin resistance, and so on. The incidence of SA in untreated diabetic patients could reach up to 50%. Body mass index (BMI) of 30 kg/m^2 or higher significantly elevates the risk of SA.[22] Therefore, it is necessary to reduce the levels of androgen, LH, and blood glucose; mitigate insulin resistance; and lower the BMI before pregnancy.

As for patients with HPRL, prolactin level should be reduced within normal range before pregnancy, and the minimum dose of bromocriptine should be applied during gestation

until the end of the 12th week of gestation. The Cochrane Collaboration reviewed previous literatures in 2016 and only included a randomized controlled trial with a small sample size of 352 cases, which indicated that the application of bromocriptine before and during pregnancy could significantly lower the rate of SA and increase live birth rate.[23,24]

Infectious factors

Less than 4% of RSAs are caused by infectious factors. Several mechanisms work in theory as follows: toxins produced by virus, bacteria, and the natural killer (NK) cells induce uterine contraction; damage the maternal–fetal interface; and cause acute infection of endometrium, placenta, fetus, and amniotic membrane, which lead to the occurrence of SA, fetal anomalies, premature membrane rupture, or fetal death. Thus, SA could be attributable to the infection of maternal–fetal interface. Positivity for *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Chlamydia trachomatis*, bacterial vaginosis, and TORCH from cervical secretions accounts for a relatively high ratio among healthy group. However, owing to the existence of cervical and maternal–fetal barriers, the occurrence of infection in the maternal–fetal interface is reduced, and thus its relationship with RSA is unclear. Therefore, general screening and treatment of the above-mentioned pathogens is not recommended. Treatment should be combined with specific medical history.

A previous study including 142 patients with RSA found that 67.6% of those patients diagnosed with chronic endometritis by hysteroscopy and 42.9% of them are confirmed by pathological examination, and suggested that chronic endometritis is a high-risk factor for RSA.[25] The European guideline in 2017 recommended that patients with RSA should undergo endometrial biopsy before pregnancy to determine whether there is chronic endometritis.

Hereditary thrombophilia

Hereditary thrombophilia can be defined as a congenital defect of blood coagulation that results in the formation of thrombosis, including the gene mutation of coagulation factor V, protein C deficiency, protein S deficiency, antithrombin deficiency, abnormal fibrinogenemia, prothrombin G20210A gene mutation, and hyperhomocysteinemia (methylenetetrahydrofolate gene mutation). A hypercoagulable state in pregnancy will induce hereditary thrombophilia and cause SA. Thrombophilia is a systematic thrombotic disease, of which the main clinical manifestation is thrombosis, mainly venous thrombosis. The relationship between hereditary thrombophilia and RSA is unclear. A meta-analysis in 2015 indicated that the mutation of coagulation factor V increased the risk of RSA with an odds ratio value of 1.68 (95% confidence interval, 1.16–2.44).[26] Another study demonstrated that methylenetetrahydrofolate gene mutation, protein C deficiency, and antithrombin deficiencies did not increase the RSA rate.[27]

Thrombosis screening should be performed for RSA patients with a history of thrombus. Controversies exist over whether to apply normal screening to detect thrombophilia for RSA patients with no symptoms of systematic thrombosis. Moreover, the efficacy and safety of heparin and aspirin administration as treatment methods should be studied and assessed.

Autoimmune diseases

Autoimmune diseases such as antiphospholipid antibody syndrome (APS), systemic lupus erythematosus (SLE), and sicca syndrome may cause dysfunction of the immune and coagulation systems during pregnancy and then induce miscarriages.

APS is a noninflammatory autoimmune disease characterized by arterial and venous thrombosis, pathological pregnancy (early miscarriage and fetal death in mid and late pregnancy), and thrombocytopenia. Moreover, antiphospholipid antibody could be detected in the serum. Therefore, RSA patients should be screened for APS laboratory indicators to determine whether the disease exists. China has published the laboratory diagnostic indexes of *The Diagnosis and Treatment Guidelines for APS* in 2011,[28] which are as follows: (1) lupus anticoagulant was found in plasma, two or more occasions at least 12 weeks apart; (2) medium-to-high IgG/IgM titers of anticardiolipin antibodies (ACLs) were detected in serum by a standardized enzyme-linked immunosorbent assay (ELISA) (IgG ACL >40 GPL; IgM ACL >40 MPL; or titer of >99th percentile), two or more occasions at least 12 weeks apart; (3) β_2-Glycoprotein-I (β_2-GP-I) antibodies were detected in serum using a standardized ELISA, two or more occasions at least 12 weeks apart (titer >99th percentile). RSA patients presented with the above laboratory indicators could be diagnosed of APS. Moreover, although antibodies such as IgA ACL, IgA β2-GP-I, anti-phosphatidyl serine, antiphosphatidyl ethanolamine, and phosphatidylserine thrombin complex are closely associated with APS, they are not specific to APS.

Those antibodies could also be detected in other autoimmune diseases, and therefore they could not be used in the diagnosis of APS. It is suggested that upon confirmation of pregnancy, RSA patients with APS should take a small dosage of aspirin plus low-molecular-weight heparin, with the former taken till the 34 weeks of gestation and the latter taken until the 6 weeks postpartum. Other experts suggested that the duration and dosage of aspirin and heparin should differ on the basis of the medical history of patients and whether their ASP could turn negative. Patients with no medical history of thrombophilia or with a history of only early SA could reduce the duration and dosage of the medicines.[29]

The medical conditions of patients with SLE should be fully assessed before planning a pregnancy. European League Against Rheumatism recommendations for women's health and the management of family planning, assisted reproduction, pregnancy, and menopause in patients with SLE and/or antiphospholipid syndrome were published in 2017, which recommended that SLE patients should seek risk factors before pregnancy, including SLE disease activity or recurrence, especially active nephritis, history of lupus nephritis, and presence of antiphospholipid antibodies; use safe medications such as hydroxychloroquine to control disease activity; and limit glucocorticoid exposure.[30]

Detection of antisperm, endometrial, and antiovary antibodies was not significantly associated with the diagnosis of RAS. There are great differences in test methods and accuracy,

so they should not be used as routine screening items and diagnostic and therapeutic indicators.

Unhealthy lifestyles

Unhealthy lifestyles, including smoking, overdrinking alcohol, excessive caffeine consumption, drug abuse, drug addiction, excessive labor activities, obesity, and exposure to chemical reagents, are closely associated with RSA. Patients with RSA should change these adverse lifestyles before getting pregnant.

Patients with RSA are prone to anxiety, depression, and other negative psychological problems, which will result in the recurrence of SA, and form a vicious cycle. Meticulous care and mental support for patients with RSA could lower the miscarriage rate. This includes the following: (1) establishing a professional RSA outpatient service and providing specialized medical counseling, (2) offering psychological support, (3) setting up a convenient communication platform between doctors and patients to ensure timely help for patients, (4) providing each patient ample chance to express her concern, (5) building up patients' confidence of getting pregnancy successfully again, (6) using auxiliary examinations such as ultrasonography in the first trimester once every week and closely monitoring each index, and (7) imparting good care to each patient by medical staff with patience.

Preconception care for unexplained recurrent spontaneous abortion patients

The preconception screening mentioned above could only identify the causes of half of the RSA patients, and the remaining half are unexplained RSA (URSA). The mechanism remains unclear but is mainly caused by embryo factors and maternal immune factors.

Embryo factors

About 50%–60% of early pregnancy SAs are caused by abnormal embryonic karyotypes, and the occurrence rate increases with maternal aging. A study tracked 1,309 couples with normal karyotypes and a history of RSA, of which 458 cases experienced SA again. The karyotype analysis of 234 abortuses showed that 51.3% of patients had abnormal chromosomes. Further analysis indicated that the occurrence of abnormal embryonic karyotype decreased with the increased number of previous SAs.[31] It is recommended to exanimate the RSA patients' abortuses, including G-banding karyotype analysis, single-nucleotide polymorphism, and comparative genomic hybridization.

Given the high incidence rate of abnormal embryonic karyotypes, experts have proposed IVF-ET plus preimplantation genetic screening (PGS) to examine the structure and number of embryonic chromosomes and screen out abnormal embryo, thereby lowering the SA rate. However, the research results were not ideal. A study indicated that no significant difference was found in live birth and miscarriage rates between PGS and control groups (spontaneous conception). Moreover, the average conceiving duration of PGS group is 6.5 months, which is apparently longer than that in the control group (3 months on an average).[32] Other studies focused on the cost-effectiveness analysis and found that although the cost of PGS was 100-fold more expensive than natural conception, patients who underwent PGS had significantly lower SA rate compared to patients who planned to undergo PGS but quit for concerning insufficient embryos.[33] Therefore, it is recommended to apply PGS for patients with recurrent abnormal embryonic karyotypes and take patients' conditions such as age, ovarian function, fertility status, and informed consent into consideration in clinical practice.

Maternal immune factors

Pregnancy could be considered a successful allograft, and the key factor for fetus survival is to prevent the fetus from being attacked by the maternal immune system. The imbalanced immune system of maternal–fetal interface could cause miscarriage, which involves NK cells, macrophage, Th1/Th2/Th17/Treg and other immune cells, and relevant cytokines. Several studies have screened the levels of NK cells and their toxicity; T-cell classification; and factors such as interleukin (IL) IL-2, IL-17, IL-4, and IL-6 to decide whether preconception treatment is necessary. However, the guiding role of these indexes in clinical practice remains unsure, and there is still a lack of large-sample research on the normal ranges of these indexes from normal fertile individuals.

Relevant treatments are still at the experimental stage. Thus, patients should be fully informed the following pros and cons of each treatment before being treated. (1) Immunotherapy including lymphocyte immunotherapy and IVIG. Different researches have different efficacy results of immunotherapy. In addition, blood samples may theoretically have the risk of transmitting hematogenous diseases and causing autoimmune diseases, thus the safety of immunotherapy is being debated. (2) Anticoagulation therapy, including application of aspirin and heparin. A systematic review of Cochrane Collaboration in 2014 indicated that there is no evidence suggesting the usage of anticoagulants for benefiting URSA, and the combined use of anticoagulants will even increase the risk of bleeding.[34] (3) Small-sample studies have proposed the application of TNF-α antagonist and granulocyte colony-stimulating factor to treat URSA, but the efficacy and safety are unclear.

Conclusion

The occurrence rate of RSA has an increasing trend in recent years, with complex pathogenesis, limited treatment therapies, and complicated management in clinical practice. Therefore, we call on clinicians to fully master relevant knowledge of RSA, screen and assess the pathogenesis of patients before planned pregnancy, offer reasonable suggestions, and provide preconception management and postpartum guidance in order to prevent the miscarriage rate and pregnancy complications such as the formation of thrombus. However, overtreatment of RSA should be prevented. Owing to the undefined pathogenesis of RSA, more basic research studies are required for further clarification. In terms of clinical research on treatment, large-sample randomized comparative studies are necessary to explore beneficial and evidence-based treatments.

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Conflicts of interest

There are no conflicts of interest.

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