ABSTRACT

Background This study aimed to assess whether pregnancy and puerperium were associated with the risk of brain arteriovenous malformation (bAVM) haemorrhage. Methods A retrospective review was conducted in Xiangya Hospital, Central South University from January 2012 to December 2021. A case–crossover design was adopted to calculate the incidence density of bAVM-related haemorrhage among female patients in risk (pregnancy and puerperium) and control (non-pregnancy and non-puerperium) periods, according to four scenarios observed in different populations (scenario I: patients with haemorrhagic bAVM of all ages; scenario II: patients with haemorrhagic bAVM of all ages, with at least one previous pregnancy; scenario III: patients with haemorrhagic bAVM who are of reproductive age (15–45 years); scenario IV: patients with haemorrhagic bAVM of reproductive age (15–45 years), with at least one previous pregnancy. Next, a comprehensive literature aggregation (up to April 2022) was performed for evidence synthesis. Results Among the 311 female patients with haemorrhagic bAVM, a significant haemorrhage risk during pregnancy and puerperium was found in Scenarios I (relative risk [RR], 2.08; 95% CI, 1.28 to 3.39), II (RR, 3.21; 95% CI, 1.95 to 5.31) and IV (RR, 2.92; 95% CI, 1.73 to 4.93); however, a suggestive risk was found in scenario III (RR, 1.62; 95% CI, 0.99 to 2.67). Evidence synthesis revealed a consistent haemorrhage risk among patients of all ages (RR, 3.15; 95% CI, 1.93 to 5.15) and those of reproductive age (RR, 1.29; 95% CI, 0.89 to 1.86). Conclusion Compared with most previous studies, a higher but relatively moderate risk for bAVM-related haemorrhage was identified during pregnancy and puerperium. Individualised prevention and treatment strategies should be preferred when neurosurgeons make clinical decisions.

INTRODUCTION

Brain arteriovenous malformation (bAVM) is a relatively rare disease with an estimated incidence of approximately 1 per 1 00 000 patient-years. bAVM rupture leads to intracranial haemorrhage and a series of neurological deficits, with the rates of functional dependence and fatality increasing over time. It has been reported that several genetic, demographic and angiographic factors could potentially increase the haemorrhage risk of bAVM, including prior haemorrhage, deep lesion location, large lesion size and some genetic variations.

Recently, several characteristics and behaviours of patients were identified as trigger factors for intracranial haemorrhage. It was found that various factors could suddenly increase blood pressure and trigger acute vessel rupture, resulting in intracranial haemorrhage, which exhibited as emotional changes, vigorous activity, sexual activity and Valsalva manoeuvres. A case–crossover study (CCOS) design treats every participant as their own control to avoid individual differences, and this approach is widely used to test trigger factors. Since Robinson et al first reported an increased bAVM-related haemorrhage rate in females during pregnancy, pregnancy and...
puerperium have been considered as potential trigger factors. Existing CCOSs have suggested a potential association of pregnancy and puerperium with bAVM-related haemorrhage in female patients.\(^7\) However, consensus could not be achieved. Several studies\(^7\) showed a higher annual bAVM-related haemorrhage rate in pregnant women compared with that in non-pregnant women (OR>4.0), whereas Horton et al.\(^11\) Liu et al.\(^12\) and Zhu et al.\(^7\) described contrary results; moreover, Liu et al.\(^2\) identified a significantly protective factor (OR, 0.71; 95% CI, 0.65 to 0.86) in the Chinese population. This inconsistency hinders the ability to make clinical recommendations. Most existing studies were highly heterogenous and included relatively small sample sizes because of the low incidence of the disease.\(^7\) Moreover, the inclusion criteria and the risk period (pregnancy and puerperium) and control period (non-pregnancy) varied across different studies. Thus, it remains unclear whether pregnancy and puerperium are trigger factors for bAVM-related haemorrhage.

To further assess the exposure effect of pregnancy and puerperium on bAVM-related haemorrhage, four CCOS scenarios in different populations were examined in this study. Next, comprehensive literature aggregation and evidence synthesis were performed by systematic review and meta-analysis to investigate the association between pregnancy and puerperium and bAVM-related haemorrhage, with an aim to provide a recommendation for clinical decisions, as well as the studies on trigger factors of acute cerebrovascular events in CCOS design.

**MATERIALS AND METHODS**

**Study population**

We performed a retrospective review of the medical records in Xiangya Hospital, Central South University from January 2012 to December 2021. All female bAVM patients with at least one haemorrhage presentation and complete clinical data were included. bAVM-related haemorrhage was diagnosed via angiography (CT angiography or digital subtraction angiography) or a histopathological examination. The results were required to be independently interpreted by at least a neurosurgeon, radiologist or pathologist. Patients with other vascular diseases, such as dural arteriovenous fistulae, spinal AVM, moyamoya disease or hereditary diseases (hereditary haemorrhagic telangiectasia, Marfan’s syndrome), were excluded. Written informed consent was obtained when they were admitted, and individual demographic, clinical and obstetric characteristics were collected at the time of treatment (for microsurgery or embolism) or at the last follow-up (for patients undergoing radiosurgery or with non-invasive treatment). Two independent authors collected medical records and angiographic imaging. Disagreements were resolved by consensus through interpretation by the third author.

**Study design**

Considering the discrepancy among the study populations and results in the previous studies, we adopted a CCOS design in our current study using four different populations to test the robustness of the results in different populations. The analysis focused on female haemorrhagic bAVM patients of all ages, regardless of whether they had experienced gestation (scenario I) and patients with at least one gestation within the same age group (scenario II). Next, female haemorrhagic bAVM patients of reproductive age (15–45 years) (scenario III) and those with at least one gestation in the same age group (scenario IV) (figure 1) were examined. The incidence density of haemorrhage in the risk and control periods was calculated for these populations.

![Figure 1](http://svn.bmj.com)  
Examples of the designs of case–crossover study including four scenarios. The age indicated the time when the patients received treatment (for microsurgery or embolism) or last follow-up (for radiosurgery or with non-invasive treatment), and haemorrhage could present at any time before this age. bAVM, brain arteriovenous malformation.
The risk period contained periods of pregnancy (40-week gestation and 6-week puerperium) and abortion (6-week abortion and 6-week postabortion interval). The control period was calculated as follows in the four scenarios: For participants of all ages (scenarios I and II), the control period was defined as the age at the time of treatment or last follow-up after subtracting the risk period. For participants of reproductive age (scenarios III and IV), the control period was defined as the age at the time of treatment or last follow-up, subtracting both the risk period and 15 years. Regarding the different clinical definitions of the periods, two recognised pregnant periods (40-week gestation and 6-week or 12-week puerperium) and two recognised abortion periods (6-week or 12-week abortion and 6-week postabortion interval) were used for a sensitivity analysis to explore whether there was any difference among the results in the distinct definitions and evaluate the robustness of the results in the current study.

**Comprehensive literature aggregation**

A comprehensive literature aggregation was conducted for potentially related articles up to April 2022. The detailed search strategy and inclusion/exclusion criteria are presented in the supplemental materials (online supplemental materials and methods).

**Statistical analysis and evidence synthesis**

Statistical analysis was conducted using STATA V.14.0 (Stata Corporation, Texas, USA). The calculated incidence densities of haemorrhage in the risk and control periods were for the Poisson rate ratio test to compare the difference. In comprehensive evidence synthesis, the number of haemorrhages per person-year in the risk and control periods was compared in random-effect models (Mantel-Haenszel heterogeneity) to obtain relative risks (RRs) and 95% CIs. Cochran’s Q test and Higgins’ $I^2$ statistic were used to assess the heterogeneity among studies. Z test was used to determine the significance of pooled RRs. We set $p<0.05$ as statistical significance. Sensitivity analysis was used to obtain pooled RRs of the remaining studies after excluding studies one by one (detailed methods are described in our previous study13). Attributable risk percent (ARP) investigated the extent to which pregnancy and puerperium could be attributed to haemorrhage in bAVM:

$$\text{ARP} = \frac{\text{RR}_{\text{risk}} - 1}{\text{RR}_{\text{risk}}} \times 100\%.$$

**Data availability statement**

Data are available on reasonable request.

**RESULTS**

**Characteristics of patients**

After retrieving the medical records, 1326 individuals with bAVM were identified, of whom 452 were women with complete clinical data. We included 311 women with a history of bAVM-related haemorrhage (scenario I), of whom 161 had at least one incidence of gestation (scenario II). There were 186 women aged 15–45 years (scenario III), among whom 106 had at least one incidence of gestation (scenario IV). All cases were sporadic and without bAVM family history. A detailed flow chart is depicted in figure 2; the characteristics of participants are listed in table 1 and online supplemental table 1.

**Association of pregnancy and puerperium with bAVM-related haemorrhage risk**

Scenario I, which focused on female patients of all ages, showed a higher haemorrhage risk during pregnancy and puerperium (RR, 2.08; 95% CI 1.28 to 3.39). Similar results were observed among female patients of all ages who had at least one gestation in scenario II (RR, 3.21; 95% CI, 1.95 to 5.31) and among patients of reproductive age with at least one gestation in scenario IV (RR, 2.72; 95% CI,
We found a suggestive risk for scenario III, which included women of reproductive age (RR, 1.62; 95% CI, 0.99 to 2.67) (Table 2). Sensitivity analysis in each scenario, conducted according to different definitions of the pregnancy and abortion periods, yielded consistent and robust results (online supplemental table 2).

Comprehensive aggregation and evidence synthesis

Ten related eligible studies7 9-12 14-18 were identified through comprehensive literature retrieval (online supplemental figure 1). This included nine studies with CCOS and one study including both a CCOS and self-control case series (details in Table 3).

Substantial heterogeneity (I² >83.5%; Cochran Q test p value<0.001) was identified when combining the existing studies and the current study focusing on either female haemorrhagic bAVMs of all ages or reproductive age (online supplemental figure 2A,B).

Given that the study design might be the source of heterogeneity, comprehensive evidence synthesis was conducted by combining studies with similar populations and definitions of risk and control periods (Table 4). Four studies7 9 10 16 included female bAVM cases in patients of all ages. Since their study designs were similar to that of the scenario I of our study, they were combined and analysed. However, substantial heterogeneity remained (I², 57.7%; p², 0.050) (online supplemental figure 2C). Further subgroup analysis was performed according to the nationalities included in the studies, as discrepancies were identified across different populations. Studies in American populations showed a much stronger association of pregnancy and puerperium with bAVM-related haemorrhage risk than those in Asian (Chinese or Japanese) populations (RR, 4.99; 95% CI, 2.97 to 8.36; ARP, 79.94%; vs RR, 2.14; 95% CI, 1.47 to 3.10; ARP, 53.16%) (Figure 3A). Five studies11 12 15 17 18 only recruited females of reproductive age with bAVM. Despite their different definitions of reproductive age, their study designs were close to that of scenario III of our study, hence, results from their studies were combined. Similar to the former analysis, the combined results were found to be more heterogeneous (I², 73.1%; p Q, 0.002) (online supplemental figure 2D). Sensitivity analysis showed that the Dutch population study by van Beijnum et al18 might be the source of heterogeneity (online supplemental figure 3). After eliminating this study, the heterogeneity was reduced (I², 33.3%; p Q, 0.200) and a potential increased risk was illustrated (RR, 1.29; 95% CI, 0.89 to 1.86; ARP, 22.24%) (Figure 3B).

DISCUSSION

Using a CCOS design, this study explored the association between pregnancy and puerperium and the risk of bAVM-related haemorrhage in the Chinese population. It then comprehensively synthesised the currently available evidence using a systematic review and meta-analysis. The original study yielded a

Table 1 Haemorrhagic and pregnancy characteristics of patients with brain arteriovenous malformation patients with presentation of haemorrhage

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Haemorrhagic in risk period (n=17)</th>
<th>Haemorrhagic patients of all ages (scenario I, n=311)</th>
<th>Haemorrhagic patients of all ages with at least one previous pregnancy (scenario II, n=161)</th>
<th>Haemorrhagic patients of reproductive age (scenario III, n=186)</th>
<th>Haemorrhagic patients of reproductive age with at least one previous pregnancy (scenario IV, n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>27.00 (5.90)</td>
<td>28.15 (16.11)</td>
<td>40.37 (12.57)</td>
<td>27.23 (8.57)</td>
<td>32.88 (6.83)</td>
</tr>
<tr>
<td>Current bAVM rupture, n (%)</td>
<td>17 (100)</td>
<td>277 (89.7)</td>
<td>143 (88.8)</td>
<td>165 (89.9)</td>
<td>94 (88.7)</td>
</tr>
<tr>
<td>Count of bAVM rupture, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 (100)</td>
<td>302 (97.1)</td>
<td>156 (96.9)</td>
<td>179 (96.3)</td>
<td>102 (96.2)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>7 (2.2)</td>
<td>3 (1.9)</td>
<td>6 (3.2)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
<td>2 (1.2)</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Pregnancy count at obliteration or the last follow-up, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (58.8)</td>
<td>163 (52.4)</td>
<td>13 (8.1)</td>
<td>93 (50.0)</td>
<td>13 (12.3)</td>
</tr>
<tr>
<td>1</td>
<td>6 (35.3)</td>
<td>84 (27.0)</td>
<td>84 (52.2)</td>
<td>67 (36.0)</td>
<td>67 (36.2)</td>
</tr>
<tr>
<td>2</td>
<td>1 (5.9)</td>
<td>47 (16.0)</td>
<td>47 (30.5)</td>
<td>22 (11.8)</td>
<td>22 (20.8)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>14 (4.5)</td>
<td>14 (8.7)</td>
<td>4 (2.1)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>3 (1.0)</td>
<td>3 (1.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abortion count at obliteration or the last follow-up, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (58.8)</td>
<td>252 (81.0)</td>
<td>102 (63.4)</td>
<td>151 (81.2)</td>
<td>71 (67.0)</td>
</tr>
<tr>
<td>1</td>
<td>6 (35.3)</td>
<td>53 (17.1)</td>
<td>53 (32.9)</td>
<td>31 (16.7)</td>
<td>31 (29.2)</td>
</tr>
<tr>
<td>2</td>
<td>1 (5.9)</td>
<td>5 (1.6)</td>
<td>5 (3.1)</td>
<td>3 (1.6)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

bAVM, brain arteriovenous malformation.
relatively consistent result in four different scenarios, an increased risk of bAVM-related haemorrhage during pregnancy and puerperium. Through the systematic review and meta-analysis, the source of the considerable heterogeneity between existing studies was identified, and it was illustrated that this discrepancy might stem from the variety in their study designs. The synthesised results of similar designs were generally consistent with those of ours, and suggestive haemorrhage risks were illustrated during pregnancy and puerperium in bAVM patients of all ages or reproductive ages.

CCOS should be the preferred choice to investigate the association between pregnancy and bAVM-related haemorrhage. This design avoids all case-specific fixed confounders such as age, chronic diseases and daily lifestyle, because every case treats itself as its own control and compares the incidence density between the risk and control periods. Among the previously performed ten studies on this topic, four claimed that they adopted a CCOS design; nevertheless, the designs of the remaining six were all similar to CCOS. A CCOS can be considered as a paired case-control or retrospective cohort study. The validity and reliability of the CCOS results highly depend on the selection of subjects and the definition of the risk and control periods. In these studies, six recruited female patients of reproductive age with bAVM, whereas the other four recruited those of all ages. The definitions of risk and control periods were varied, and the results demonstrated significant heterogeneity (I^2 >80%; Cochran Q test p value<0.001). Therefore, a hypothesis that the heterogeneity might arise from the diversities of included patients, and the corresponding risk and control periods was proposed. Considering this, our CCOS design was adopted by including four different populations to test the robustness of the results in different populations.

Female haemorrhagic bAVM patients of all ages were recruited for risk estimation in scenario I. Our data showed an increased risk of haemorrhage during pregnancy and puerperium (RR, 2.08; 95% CI, 1.28 to 3.39). After data adjustment and combination, the pooled results were consistent and showed an increased risk during pregnancy and puerperium even when population discrepancy was observed (RR, 3.15; 95% CI, 1.93 to 5.15). The haemorrhage risk was higher among the American populations (RR, 4.99; 95% CI, 2.47 to 9.60) than in the Asian populations (RR, 1.59; 95% CI, 1.14 to 2.21). It should be noted that five previous studies simultaneously included non-haemorrhagic patients without previous pregnancy, which increased the person-years in the control period and potentially exaggerated the haemorrhage risk during pregnancy and puerperium. These patients should not have been included because the assessed event of bAVM-related haemorrhage did not occur and each participant failed to be treated as their own control. In contrast, scenario II could be tested as their own control.

Table 2 Haemorrhage risk of brain arteriovenous malformation during risk and control periods

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Included individuals, n</th>
<th>Risk period</th>
<th>Control period</th>
<th>Relative risk (95% CI)</th>
<th>Attributable risk per cent, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>311</td>
<td>17</td>
<td>229</td>
<td>7.44</td>
<td>2.08 (1.28 to 3.39)</td>
</tr>
<tr>
<td>II</td>
<td>161</td>
<td>17</td>
<td>220</td>
<td>7.73</td>
<td>2.40 (1.95 to 5.31)</td>
</tr>
<tr>
<td>III</td>
<td>186</td>
<td>17</td>
<td>126</td>
<td>13.48</td>
<td>8.30 (1.99 to 2.67)</td>
</tr>
<tr>
<td>IV</td>
<td>106</td>
<td>17</td>
<td>118</td>
<td>14.41</td>
<td>5.29 (1.63 to 4.57)</td>
</tr>
</tbody>
</table>

on December 10, 2023 by guest. Protected by copyright.
Table 3  Characteristics of included studies focusing on the haemorrhage of brain arteriovenous malformation during pregnancy and puerperium

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Medical centre (study period)</th>
<th>Study design</th>
<th>Included patients, n</th>
<th>Definition of risk period</th>
<th>Definition of control period</th>
<th>Risk period</th>
<th>Control period</th>
<th>Person-years</th>
<th>Incidence density (person-years)</th>
<th>Event</th>
<th>Person-years</th>
<th>Incidence density (person-years)</th>
<th>Event</th>
<th>Person-years</th>
<th>Incidence density (person-years)</th>
<th>Statistical analysis</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horton et al11</td>
<td>USA</td>
<td>NA</td>
<td>Massachusetts General Hospital (1977–1986)</td>
<td>CCOS Female bAVMs receiving proton beam therapy (n=451)*</td>
<td>40-week gestation and 12-week postpartum 0.3 years (according to the average 12-week abortion and 6-week postabortion period)</td>
<td>17</td>
<td>469</td>
<td>0.035±0.005 (0.024–0.045)</td>
<td>442</td>
<td>13 766</td>
<td>0.031±0.002 (0.028–0.034)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forster et al15</td>
<td>UK</td>
<td>NA</td>
<td>Leksell Gamma Unit (1985–1991)</td>
<td>CCOS Female bAVMs from 15 to 45 years receiving treatment of SRS (n=191)*</td>
<td>40-week gestation</td>
<td>15</td>
<td>187</td>
<td>0.093</td>
<td>207</td>
<td>34 02</td>
<td>0.045</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fujita et al16</td>
<td>Japan</td>
<td>NA</td>
<td>University of Tsukuba (1979–1995)</td>
<td>CCOS Female bAVMs from 15 to 45 years receiving treatment of SRS (n=42)*</td>
<td>40-week gestation and 12-week postpartum 39-week gestation</td>
<td>3</td>
<td>46</td>
<td>0.066±0.036 (0.020–0.180)</td>
<td>5</td>
<td>341</td>
<td>0.015±0.007 (0.004–0.031)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley and Rose10</td>
<td>USA</td>
<td>NA</td>
<td>Brigham and Women’s Hospital (2002–2010)</td>
<td>CCOS Female bAVMs (n=58)*</td>
<td>39-week gestation</td>
<td>5</td>
<td>47</td>
<td>0.108</td>
<td>28</td>
<td>24 61</td>
<td>0.011</td>
<td>NA</td>
<td>7.91 (2.64 to 23.71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu et al12</td>
<td>China</td>
<td>Asian</td>
<td>Beijing Tiantan Hospital (1990–2010)</td>
<td>CCOS Female haemorrhagic bAVMs from 18 to 40 years (n=393)†</td>
<td>Gestation and 6-week postpartum (10 months) Age at treatment subtracting both risk period and 18 years</td>
<td>12</td>
<td>361</td>
<td>0.033</td>
<td>441</td>
<td>10 627</td>
<td>0.043</td>
<td>Mantel–Haenszel estimator</td>
<td>0.71 (0.61 to 0.82)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonetti et al13</td>
<td>USA</td>
<td>NA</td>
<td>University of Pittsburgh (1987–2012)</td>
<td>CCOS Female bAVMs from 15 to 40 years receiving treatment of radiotherapy (n=253)*</td>
<td>40-week gestation and 12-week postpartum interval Age at the last follow-up subtracting both risk period and age at radiosurgery</td>
<td>2</td>
<td>18</td>
<td>0.111</td>
<td>20</td>
<td>810</td>
<td>0.025</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Beijnum et al18</td>
<td>Netherlands</td>
<td>NA</td>
<td>VUMC Amsterdam, AMC Amsterdam, Leiden UMC, UMC Utrecht (1990–2006)</td>
<td>CCOS Female bAVMs from 16 to 41 years (n=95)*</td>
<td>39-week gestation</td>
<td>17</td>
<td>56</td>
<td>0.304</td>
<td>78</td>
<td>12 311</td>
<td>0.063</td>
<td>NA</td>
<td>6.8 (3.6 to 13.0) for CCOS, 7.1 (3.4 to 13.0) for SCCSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td></td>
<td></td>
<td>SAIVMs (1999–2003, 2006–2010)</td>
<td>Female bAVMs with complete baseline data (n=279)*</td>
<td>40-week gestation and 6-week postpartum Age at treatment of AVM or last follow-up subtracting risk period</td>
<td>3</td>
<td>35</td>
<td>0.086</td>
<td>41</td>
<td>597</td>
<td>0.069</td>
<td>NA</td>
<td>1.3 (0.39 to 4.1) for CCOS, 1.7 (0.10 to 4.4) for SCCSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porras et al9</td>
<td>USA</td>
<td>White 61.1%, black 21.9%, Hispanic 3.3%, Asian 2.2%, other 11.5%</td>
<td>Johns Hopkins Hospital (1990–2015)</td>
<td>OCOS Female bAVMs with complete baseline data (n=279)*</td>
<td>6-week abortion and 6-week postabortion period Age at treatment of AVM or last follow-up subtracting risk period</td>
<td>9</td>
<td>159</td>
<td>0.057 for all patients; 0.070 for patients from 15 to 50 years</td>
<td>140</td>
<td>10 668</td>
<td>0.013 for both all patients and those from 15 to 50 years</td>
<td>Poisson regression</td>
<td>4.43 (1.98 to 9.05) for all patients; 5.61 (2.48 to 11.18) for patients from 15 to 50years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued


### Table 3  Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Medical centre (study period)</th>
<th>Included patients, n</th>
<th>CCOS Female bAVMs from 15 to 45 years</th>
<th>Study Design</th>
<th>Included patients, n</th>
<th>CCOS Female bAVMs with complete baseline data</th>
<th>Person-years</th>
<th>Incidence density (person-years)</th>
<th>Event</th>
<th>Person-years</th>
<th>Incidence density (person-years)</th>
<th>Statistical analysis</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu et al</td>
<td>China</td>
<td>Asian</td>
<td>Changhai Hospital (2006–2017)</td>
<td>8</td>
<td>148</td>
<td>0.054</td>
<td>214</td>
<td>7336</td>
<td>0.029</td>
<td>Dichotomous variables</td>
<td>1.90</td>
<td>(0.92 to 3.93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al</td>
<td>USA</td>
<td>White</td>
<td>SID for California (2005–2011), Florida (2005–2014), New York (2005–2014)</td>
<td>36</td>
<td>36</td>
<td>0.064 (0.043–0.084)</td>
<td>11</td>
<td>11</td>
<td>0.019 (0.008–0.031)</td>
<td>Poisson regression</td>
<td>3.27</td>
<td>(1.67 to 6.49)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aIncluded patients regardless of haemorrhage presentation.
†Included patients with haemorrhage presentation.
bAVMs, brain arteriovenous malformations; CCOS, case-crossover study; NA, not available; RR, relative rate; SAIVMs, Scottish Audit of Intracranial Vascular Malformations study; SCCSS, self-controlled case series study; SID, Healthcare Cost and Utilisation Project State Inpatient Databases; SRS, stereotactic radiosurgery.
## Table 4

Pooled ORs (95% CIs) in comprehensive evidence synthesis for the association between pregnancy/puerperium and brain arteriovenous malformation haemorrhage after adjustment

<table>
<thead>
<tr>
<th>Grouping criterion</th>
<th>Included study</th>
<th>Sample size</th>
<th>Event</th>
<th>Adjusted person-years</th>
<th>Event</th>
<th>Adjusted person-years</th>
<th>Weight, %</th>
<th>RR (95% CI)</th>
<th>Attributable risk per cent, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female bAVM Patients Included</td>
<td>Fujita et al16</td>
<td>42</td>
<td>3</td>
<td>41</td>
<td>20</td>
<td>1292</td>
<td>12.90</td>
<td>4.24 (1.42 to 12.71)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Bradley and Rose10</td>
<td>58</td>
<td>5</td>
<td>55</td>
<td>28</td>
<td>2453</td>
<td>17.38</td>
<td>6.91 (2.96 to 16.14)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Porras et al9</td>
<td>270</td>
<td>9</td>
<td>159</td>
<td>140</td>
<td>10 668</td>
<td>22.06</td>
<td>4.11 (2.14 to 7.89)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Zhu et al8</td>
<td>264</td>
<td>8</td>
<td>148</td>
<td>214</td>
<td>7336</td>
<td>20.85</td>
<td>1.82 (0.91 to 3.67)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Our study</td>
<td>311</td>
<td>17</td>
<td>229</td>
<td>305</td>
<td>8523</td>
<td>26.80</td>
<td>2.02 (1.25 to 3.26)</td>
<td>–</td>
</tr>
<tr>
<td>Total (I², 57.7%; pQ, 0.050; pZ, &lt;0.001)</td>
<td></td>
<td>945</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>3.15 (1.93 to 5.15)</td>
<td>68.26</td>
</tr>
<tr>
<td></td>
<td>Forster et al15</td>
<td>191</td>
<td>15</td>
<td>187</td>
<td>207</td>
<td>3402</td>
<td>28.80</td>
<td>1.27 (0.77 to 2.11)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Liu et al12</td>
<td>393</td>
<td>12</td>
<td>400</td>
<td>441</td>
<td>11 767</td>
<td>25.44</td>
<td>0.81 (0.46 to 1.42)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Tonetti et al17</td>
<td>253</td>
<td>2</td>
<td>18</td>
<td>20</td>
<td>800</td>
<td>6.33</td>
<td>4.13 (1.02 to 16.72)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>van Beijnum et al18 Scotland</td>
<td>44</td>
<td>3</td>
<td>41</td>
<td>41</td>
<td>635</td>
<td>9.10</td>
<td>1.12 (0.36 to 3.49)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Our study</td>
<td>186</td>
<td>17</td>
<td>126</td>
<td>177</td>
<td>2132</td>
<td>30.25</td>
<td>1.57 (0.97 to 2.55)</td>
<td>–</td>
</tr>
<tr>
<td>Total (I², 33.3%; pQ, 0.200; pZ, 0.185)</td>
<td></td>
<td>1067</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>1.29 (0.89 to 1.86)</td>
<td>22.24</td>
</tr>
</tbody>
</table>

pQ value for Q test; pZ value for Z test; the RR and 95% CI were calculated in random effects model.

RR, relative risks.
females of this age share similar characteristics and could get pregnant; hence, theoretically, the differences would not affect the results as much. Remarkably, Tonetti et al. recruited a reproductive bAVM cohort that underwent radiosurgery and required follow-up. The risk was estimated by calculating the haemorrhage incidence densities in pregnant and non-pregnant periods during the follow-up rather than according to reproductive age.

Similarly, 106 reproductive-aged haemorrhagic bAVM females with at least one previous pregnancy were included for further analysis in scenario IV. The significantly increased haemorrhage risk (RR, 2.923; 95% CI, 1.734 to 4.928) was also higher compared with that in scenarios III, with the same reason for the difference between scenarios I and II, while haemorrhagic bAVM patients of reproductive age simultaneously with at least one previous pregnancy performed better in establishing a self-control model and matching CCOS design. However, no study with a design similar to that of scenario IV has been published; the sample size should be expanded in the future.

Lee et al. recruited a new population of 568 female bAVM patients, who had at least one pregnancy, from three medical centres in the USA. Incidence densities of intracranial haemorrhage were compared between the risk period of the first 52 weeks of pregnancy and delivery and the control period of 52 weeks before the first pregnancy. They reported a 6.4% incidence density of haemorrhage during the risk period, which was relatively higher than the 1.9% reported 1 year prior to pregnancy, which resulted in increased haemorrhage risk (RR, 3.27; 95% CI, 1.67 to 6.43). This study design was similar to that of a retrospective cohort study, and the authors described it as a cohort-crossover study. Because the limited control period was close to the risk period, the physical condition and behaviour of the patients would be relatively similar; therefore, this design was also preferable as it reduced the confounders from other trigger factors. However, this study defined bAVMs as ‘747.81 Anomalies of Cerebrovascular System’ using the International Classification of Diseases-9 diagnosis code, highlighting the information bias by recruiting patients with other cerebrovascular abnormalities. It was not certain whether the included patients had been treated before, as a treatment of microsurgery or embolism would substantially modify the haemorrhage risk of bAVM. Additionally, only patients with a pregnancy history were recruited, but usually those who suffered a bAVM-related haemorrhage in the control period would not choose to get pregnant soon within 1 year, which resulted in a selection bias. The incidence density of haemorrhage in the control period was underestimated and a more significant RR was achieved to magnify the haemorrhage risk during pregnancy and puerperium.

This study identified a moderately higher haemorrhage risk of bAVM females during pregnancy and

![Figure 3](https://example.com/figure3.png)

**Figure 3** Forest plots of haemorrhage risk for female patients with brain arteriovenous malformation during pregnancy and puerperium: (A) Subgroup (according to populations) analysis performed among participants of all ages. (B) Meta-analysis performed among participants of reproductive age excluding the Dutch populations from the study by van Beijnum et al.

consideration, which underestimated the person-years of the risk period and subsequently overestimated the RR of pregnancy and puerperium.

Regarding the Chinese population, our results were consistent with those of Zhu et al. (OR, 1.90; 95% CI, 0.92 to 3.93) but conflicted with the conclusion of another study. Liu et al. retrospectively investigated 395 female reproductive-aged patients with haemorrhagic bAVM admitted to Beijing Tiantan Hospital in the past 50 years and found that pregnancy and puerperium were protective factors (OR, 0.71; 95% CI, 0.61 to 0.82). We speculated that the study in the Tiantan hospital had an admission bias since it is a globally renowned neuromedical centre and a specialised hospital. Patients with complicated neurological symptoms were transferred to this hospital, but emergency pregnant patients were more likely to be transferred to the general or maternity hospitals. Thus, the number of individuals with haemorrhage during the risk period was even less than that in our 10-year study, showing an underestimation of haemorrhage risk among pregnant patients.

Although researchers have given various definitions of reproductive age (15–45 years by Forster et al. and Lee et al. 18–40 years by Liu et al. 15–40 years by Tonetti et al. and 16–41 years by van Beijnum et al.8),
puerperium, and explained potential reasons behind the published results appearing controversial in methodological levels. To explain the increased haemorrhage risk, it is noted that a large turbulence of blood volume and blood pressure in different hormonal statuses results in changes in haemodynamics, coagulation and vascular physiology. Previous studies also revealed that hypertensive disorders of pregnancy disturbed functions of systemic endothelial cells and the blood–brain barrier; finally, the failure of cerebral autoregulation leads to the rupture of bAVM and haemorrhagic stroke.

Several limitations should be mentioned. First, though a pooled analysis was conducted to test the robustness of the association, it could not consider all the confounding factors, which was a methodological limit of meta-analysis, and a study conducted among multiple medical centres with a larger sample size is required in the future. Sufficient shared original data are important for such a low-incidence disease to obtain conclusive evidence. Further, the studies obtained in the systematic review process were not sufficient, which resulted in challenges in conducting subgroup analyses, sensitivity analyses and assessment of publication bias, as well as assessing their effect on the combined results. In this study, individual-specific characteristics were not required for comparison, as the estimation was made within each patient case. Many transient exposures and trigger factors that may increase the haemorrhage risk of bAVM were not assessed in this study because of a lack of clinical data. Thus, medical workers should pay more attention to collecting related information, so that future studies can perform multiple comparisons to explore more trigger factors and reduce confounders. Finally, the study design was based on an ideal assumption that the incidence densities of bAVM-related haemorrhage were constant during the defined intervals. However, this is likely unrealistic in practical research.

Conclusion
This study suggested that an increased bAVM-related haemorrhage risk during pregnancy and puerperium through different analysis strategies and evidence synthesis. Still, this risk was relatively moderate compared with previous studies’ results. In clinical decision-making, individualised prevention and treatment strategies are preferred. Patients contemplating pregnancy should exercise caution according to their intentions, individual disease characteristics and the experience of their clinicians.

Contributors JL: data curation, statistical analysis, investigation, validation, resources and software, writing for original draft, writing for review and editing. HZ: data curation, investigation, CL: statistical analysis. YC: statistical analysis. YL: data curation, investigation, validation, funding acquisition. DJ: funding acquisition. WJ: funding acquisition. JY: guarantor, project administration and supervision, methodology, funding acquisition, statistical analysis, writing for original draft, writing for review and editing.

Funding This study was supported by the grants from the Hunan Province Nature Science Foundation, China (2021JJ30911, 2021JJ31077, 2021JJ31121), Financial Science and Technology Project of Hunan Province, China (42200008), Central South University Case Database Construction Project for Graduate Students, China (2020ALK24).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Medical Ethics Committee of XiangYa School of Public Health, Central South University, China (XYGW-2020-90). The consent was not required again as this was a retrospective study using deidentified data of discharged patient.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs Jyun Lu http://orcid.org/0000-0002-3803-4068 Chun Luo http://orcid.org/0000-0001-9935-9467 Yuxin Gu http://orcid.org/0000-0002-6775-8399 Yifei Li http://orcid.org/0000-0002-7393-8453 Dun Yuan http://orcid.org/0000-0002-7593-8453 Wei Jiang http://orcid.org/0000-0003-1570-0854 Junxia Van http://orcid.org/0000-0001-6667-1613

REFERENCES


Supplemental Materials

Supplemental Methods

A systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Human Genome Epidemiology Network guidelines. A total of five databases, including PubMed, Embase, Web of Science, China National Knowledge Infrastructure, and Wanfang Databases, were searched without language restrictions for candidate articles up to April 2022. The search terms were (Cerebral AVM OR cerebral arteriovenous malformation OR brain AVM OR brain arteriovenous malformation) AND (pregnancy OR pregnancies OR gestation).

The work of study selection and data extraction were conducted by two independent authors, and any disagreement was resolved by discussion or re-evaluation by a third author. We included all the case-series studies and cohort studies that assessed the haemorrhage risk of bAVM during periods of pregnancy and non-pregnancy in consecutive female cases. Studies with following characteristics were excluded: (1) studies focusing on other vascular malformations such as spine arteriovenous malformation, dural arteriovenous fistulas, cavernous malformations and vein of Galen malformations; (2) studies without clear definitions (recruited individuals, risk and control periods) or sufficient data to calculate relative risks (RRs) and 95% confidence interval (95%CI); (3) conference abstracts, editorials, letters, comments, review articles, case reports, and animal/cellular experimental studies. If multiple studies were published containing the same cohort, the one with the largest sample size were included for further analysis.

The person-years in risk and control periods were firstly adjusted using the numbers of pregnancy and abortion published in articles according to the definition of pregnancy (40-week gestation and 6-week puerperium) and abortion (6-week abortion and 6-week postabortion interval) in this study, then meta-analysis was conducted.
References


Supplemental Figures

Supplemental Figure 1. Flowchart of literature search results and study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
Supplemental Figure 2. Forest plots of haemorrhage risk for female brain arteriovenous malformation patients in risk and control periods: (A, B) Meta-analysis performed combining ten published studies with either Scenario I or III in present study; (C) Meta-analysis analysis performed among participants of all ages; (D) Meta-analysis performed among participants of reproductive age (15 - 45 years).
Supplemental Figure 3. The sensitive analysis for the meta-analysis among participants of reproductive age (15 - 45 years).
## Supplemental Tables

**Supplemental Table 1.** Clinical characteristics of brain arteriovenous malformation patients with presentation of haemorrhage

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients with haemorrhage in Risk Period (n=17)</th>
<th>Haemorrhagic Patients of reproductive age with at Least One Previous Pregnancy (Scenario IV, n=106)</th>
<th>Haemorrhagic Patients of all ages with at Least One Previous Pregnancy (Scenario III, n=186)</th>
<th>Haemorrhagic patients of all ages (Scenario I, n=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race (%)</td>
<td>Asian (100.0)</td>
<td>Asian (100.0)</td>
<td>Asian (100.0)</td>
<td>Asian (100.0)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>3 (17.6)</td>
<td>17 (16.0)</td>
<td>28 (15.1)</td>
<td>22 (13.7)</td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>2 (11.8)</td>
<td>12 (11.3)</td>
<td>26 (15.1)</td>
<td>23 (14.3)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>0 (0)</td>
<td>4 (3.8)</td>
<td>4 (2.1)</td>
<td>9 (5.6)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>4 (23.5)</td>
<td>15 (14.2)</td>
<td>20 (10.8)</td>
<td>27 (16.8)</td>
</tr>
<tr>
<td>Presenting bAVM Rupture, n (%)</td>
<td>17 (100)</td>
<td>94 (88.7)</td>
<td>165 (89.9)</td>
<td>143 (88.8)</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-intervention Treatment</td>
<td>1 (5.9)</td>
<td>8 (7.6)</td>
<td>11 (5.9)</td>
<td>13 (8.1)</td>
</tr>
<tr>
<td>Microsurgery Only</td>
<td>15 (88.2)</td>
<td>80 (75.5)</td>
<td>131 (70.4)</td>
<td>118 (73.3)</td>
</tr>
<tr>
<td>Embolism Only</td>
<td>1 (5.9)</td>
<td>10 (9.4)</td>
<td>27 (14.5)</td>
<td>20 (12.4)</td>
</tr>
<tr>
<td>Radiosurgery Only</td>
<td>0 (0)</td>
<td>3 (2.8)</td>
<td>6 (3.2)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Microsurgery &amp; Embolism</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>4 (2.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Microsurgery &amp; Radiosurgery</td>
<td>0 (0)</td>
<td>2 (1.9)</td>
<td>3 (1.6)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Embolism &amp; Radiosurgery</td>
<td>0 (0)</td>
<td>2 (1.9)</td>
<td>4 (2.1)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>4 (23.5)</td>
<td>28 (26.4)</td>
<td>40 (21.5)</td>
<td>40 (24.8)</td>
</tr>
<tr>
<td>Parietal</td>
<td>0 (0)</td>
<td>22 (20.8)</td>
<td>43 (23.1)</td>
<td>32 (19.9)</td>
</tr>
<tr>
<td>Temporal</td>
<td>5 (29.4)</td>
<td>24 (22.6)</td>
<td>52 (28.0)</td>
<td>43 (26.7)</td>
</tr>
<tr>
<td>Occipital</td>
<td>3 (17.6)</td>
<td>15 (14.2)</td>
<td>30 (16.1)</td>
<td>27 (16.8)</td>
</tr>
<tr>
<td>Basal Ganglia &amp; Thalamus</td>
<td>0 (0)</td>
<td>7 (6.6)</td>
<td>15 (8.1)</td>
<td>9 (5.6)</td>
</tr>
<tr>
<td>Corpus Callosum &amp; Hippocampus</td>
<td>1 (5.9)</td>
<td>7 (6.6)</td>
<td>15 (8.1)</td>
<td>7 (4.3)</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>1 (5.9)</td>
<td>18 (17.0)</td>
<td>25 (13.4)</td>
<td>32 (19.9)</td>
</tr>
<tr>
<td>Brain Stem</td>
<td>0 (0)</td>
<td>3 (2.8)</td>
<td>3 (1.6)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Size, cm, mean (SD)</td>
<td>2.31 (1.16)</td>
<td>2.79 (1.40)</td>
<td>2.90 (1.50)</td>
<td>2.77 (1.43)</td>
</tr>
<tr>
<td>Hemodynamic Related Aneurysm, n (%)</td>
<td>3 (17.6)</td>
<td>22 (20.8)</td>
<td>29 (15.6)</td>
<td>40 (24.8)</td>
</tr>
<tr>
<td>Deep Venous Drainage, n (%)</td>
<td>7 (41.2)</td>
<td>42 (39.6)</td>
<td>76 (40.9)</td>
<td>72 (44.7)</td>
</tr>
<tr>
<td>Thick Drainage Vein or Venous Bulb, n (%)</td>
<td>3 (17.6)</td>
<td>42 (39.6)</td>
<td>70 (37.6)</td>
<td>65 (40.4)</td>
</tr>
<tr>
<td>Spetzler-Martin Grading, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (23.5)</td>
<td>16 (15.1)</td>
<td>27 (14.5)</td>
<td>27 (16.8)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>9 (52.9)</td>
<td>46 (43.4)</td>
<td>69 (37.1)</td>
<td>65 (40.4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (17.6)</td>
<td>28 (26.4)</td>
<td>55 (29.6)</td>
<td>44 (27.4)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (5.9)</td>
<td>14 (13.2)</td>
<td>28 (15.1)</td>
<td>21 (13.0)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0 (0)</td>
<td>2 (1.9)</td>
<td>7 (3.8)</td>
<td>4 (2.5)</td>
</tr>
</tbody>
</table>

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s).
### Supplemental Table 2: Design and analysis of four scenarios on haemorrhage risk of brain arteriovenous malformation during risk and control periods in the Chinese population.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Included Individuals</th>
<th>Definition of Risk Period (Pregnancy)</th>
<th>Definition of Risk Period (Abortion)</th>
<th>Definition of Control Period</th>
<th>Risk Period</th>
<th>Control Period</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Attributable Risk Percent, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Haemorrhagic bAVM of all ages (n=311)</td>
<td>40-week gestation and 6-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting risk period</td>
<td>17 229 7.44% 305 8523 3.59%</td>
<td>2.078(1.275 - 3.387)</td>
<td>51.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td></td>
<td></td>
<td>17 255 6.66% 305 8497 3.59%</td>
<td>1.855(1.138 - 3.023)</td>
<td>46.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-week gestation and 12-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting risk period</td>
<td>17 236 7.20% 305 8516 3.59%</td>
<td>2.010(1.233 - 3.275)</td>
<td>50.25</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td></td>
<td></td>
<td>17 263 6.47% 305 8489 3.59%</td>
<td>1.799(1.104 - 2.933)</td>
<td>44.41</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Haemorrhagic bAVM of all ages with at least one previous pregnancy (n=161)</td>
<td>40-week gestation and 6-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting risk period</td>
<td>17 220 7.73% 151 6280 2.40%</td>
<td>3.214(1.946 - 5.306)</td>
<td>68.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td></td>
<td></td>
<td>17 228 7.46% 151 6272 2.41%</td>
<td>3.097(1.876 - 5.113)</td>
<td>67.71</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-week gestation and 12-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting risk period</td>
<td>17 247 8.88% 151 6253 2.41%</td>
<td>2.850(1.726 - 4.706)</td>
<td>64.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td></td>
<td></td>
<td>17 265 6.67% 151 6245 2.42%</td>
<td>2.757(1.670 - 4.552)</td>
<td>63.73</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Haemorrhagic bAVM of reproductive age (n=186)</td>
<td>40-week gestation and 6-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting both risk period and 15 yrs</td>
<td>17 126 13.48% 177 2133 8.30%</td>
<td>1.624(0.987 - 2.671)</td>
<td>38.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td></td>
<td></td>
<td>17 140 12.11% 177 2119 8.35%</td>
<td>1.450(0.881 - 2.385)</td>
<td>31.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-week gestation and 12-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting both risk period and 15 yrs</td>
<td>17 131 13.00% 177 2128 8.32%</td>
<td>1.563(0.950 - 2.571)</td>
<td>36.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td></td>
<td></td>
<td>17 145 11.73% 177 2114 8.37%</td>
<td>1.401(0.852 - 2.304)</td>
<td>28.62</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Haemorrhagic bAVM with at least one previous pregnancy of reproductive age (n=106)</td>
<td>40-week gestation and 6-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting both risk period and 15 yrs</td>
<td>17 118 14.41% 94 1777 5.29%</td>
<td>2.723(1.625 - 4.565)</td>
<td>63.28</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td></td>
<td></td>
<td>17 123 13.82% 94 1772 5.30%</td>
<td>2.605(1.554 - 4.367)</td>
<td>61.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-week gestation and 12-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting both risk period and 15 yrs</td>
<td>17 132 12.88% 94 1763 5.33%</td>
<td>2.415(1.441 - 4.049)</td>
<td>58.59</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td></td>
<td></td>
<td>17 137 12.41% 94 1758 5.35%</td>
<td>2.321(1.384 - 3.890)</td>
<td>56.92</td>
<td></td>
</tr>
</tbody>
</table>
**Supplemental Table 3**: Search strategy of potentially related literature.

<table>
<thead>
<tr>
<th>Database</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pubmed</td>
<td>(((Cerebral AVM[Title/Abstract]) OR (intracranial AVM[Title/Abstract]) OR (cerebral arteriovenous malformation[Title/Abstract]) OR (intracranial arteriovenous malformation[Title/Abstract]) OR (brain AVM[Title/Abstract]) OR (brain arteriovenous malformation[Title/Abstract]) 1924})</td>
<td>pregnant* OR pregnancy* OR gestation* 1135985</td>
<td>79</td>
</tr>
<tr>
<td>Web of Science</td>
<td>(((TS=(Cerebral AVM))OR TS=(intracranialAVM)) OR TS=(cerebralarteriovenous malformation)) OR TS=(intracranial arteriovenous malformation)) OR TS=(brainAVM) 16876</td>
<td>TS=(pregnant*) OR TS=(pregnancy*) OR TS=(gestation*) 1365599</td>
<td>577</td>
</tr>
<tr>
<td>Embase</td>
<td>cerebral avm:ab,ti OR 'intracranial arteriovenous malformation':ab,ti OR 'brain avm':ab,ti OR 'cerebral arteriovenous malformation':ab,ti OR 'intracranial avm':ab,ti OR 'brain arteriovenous malformation':ab,ti 2368</td>
<td>pregnant*:ab,ti OR 'pregnancy*:ab,ti OR 'gestation*:ab,ti 848745</td>
<td>77</td>
</tr>
<tr>
<td>CNKI</td>
<td>(SU%=CerebralAVM) OR (SU%=intracranial AVM) OR (SU%=cerebral arteriovenous malformation) OR (SU%=intracranial arteriovenous malformation) OR (SU%=brain AVM) OR (SU%=brain arteriovenous malformation) 9006</td>
<td>(SU%=pregnant) OR (SU%=pregnancy) OR (SU%=gestation) 942704</td>
<td>116</td>
</tr>
<tr>
<td>Wanfang</td>
<td>Theme:(Cerebral AVM) or Theme:(intracranial AVM) or Theme:(cerebral arteriovenous malformation) or Theme:(intracranial arteriovenous malformation) or Theme:(brain AVM) or Theme:(brain arteriovenous malformation) 4454</td>
<td>Theme:(pregnant) or Theme:(pregnancy) or Theme:(gestation) 968821</td>
<td>88</td>
</tr>
</tbody>
</table>
Supplemental Materials

Supplemental Methods

A systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Human Genome Epidemiology Network guidelines. A total of five databases, including PubMed, Embase, Web of Science, China National Knowledge Infrastructure, and Wanfang Databases, were searched without language restrictions for candidate articles up to April 2022. The search terms were (Cerebral AVM OR cerebral arteriovenous malformation OR brain AVM OR brain arteriovenous malformation) AND (pregnancy OR pregnancies OR gestation).

The work of study selection and data extraction were conducted by two independent authors, and any disagreement was resolved by discussion or re-evaluation by a third author. We included all the case-series studies and cohort studies that assessed the haemorrhage risk of bAVM during periods of pregnancy and non-pregnancy in consecutive female cases. Studies with following characteristics were excluded: (1) studies focusing on other vascular malformations such as spine arteriovenous malformation, dural arteriovenous fistulas, cavernous malformations and vein of Galen malformations; (2) studies without clear definitions (recruited individuals, risk and control periods) or sufficient data to calculate relative risks (RRs) and 95% confidence interval (95%CI); (3) conference abstracts, editorials, letters, comments, review articles, case reports, and animal/cellular experimental studies. If multiple studies were published containing the same cohort, the one with the largest sample size were included for further analysis.

The person-years in risk and control periods were firstly adjusted using the numbers of pregnancy and abortion published in articles according to the definition of pregnancy (40-week gestation and 6-week puerperium) and abortion (6-week abortion and 6-week postabortion interval) in this study, then meta-analysis was conducted.
References


**Supplemental Figures**

12th April, 2022

553 records were identified from the databases: PubMed (n=79); Embase (n=77); Web of Science (n=193); CNKI (n=116); Wanfang (n=88).

- Duplicated articles excluded (n=192)
- Exclusion for irrelevant studies by screening title and abstract (n=361)
- Full-text articles assessed for eligibility (n=18)
- Additional relevant articles added from reference lists (n=1)
- Articles included in quantitative synthesis and qualitative description (n=10)
- Excluded studies (n=28): Animal study (n=3); Case report (n=79); Comment (n=3); Conference abstract (n=4); Duplicate (n=3); Letter (n=5); Not demographic study (n=1); Not the disease (n=184); Not the outcome (n=62); Overlapped (n=1); Review (n=7).

**Supplemental Figure 1.** Flowchart of literature search results and study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
Supplemental Figure 2. Forest plots of haemorrhage risk for female brain arteriovenous malformation patients in risk and control periods: (A, B) Meta-analysis performed combining ten published studies with either Scenario I or III in present study; (C) Meta-analysis analysis performed among participants of all ages; (D) Meta-analysis performed among participants of reproductive age (15 - 45 years).
Supplemental Figure 3. The sensitive analysis for the meta-analysis among participants of reproductive age (15 - 45 years).
## Supplemental Tables

### Supplemental Table 1. Clinical characteristics of brain arteriovenous malformation patients with presentation of haemorrhage

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients with haemorrhage in Risk Period (n=17)</th>
<th>Haemorrhagic Patients of reproductive age with at Least One Previous Pregnancy (Scenario IV, n=106)</th>
<th>Haemorrhagic Patients of all ages with at Least One Previous Pregnancy (Scenario III, n=186)</th>
<th>Haemorrhagic Patients of all ages (Scenario I, n=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race (%)</td>
<td>Asian (100.0)</td>
<td>Asian (100.0)</td>
<td>Asian (100.0)</td>
<td>Asian (100.0)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>3 (17.6)</td>
<td>17 (16.0)</td>
<td>28 (15.1)</td>
<td>22 (13.7)</td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>2 (11.8)</td>
<td>12 (11.3)</td>
<td>28 (15.1)</td>
<td>23 (14.3)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>0 (0)</td>
<td>4 (3.8)</td>
<td>4 (2.1)</td>
<td>9 (5.6)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>4 (23.5)</td>
<td>15 (14.2)</td>
<td>20 (10.8)</td>
<td>27 (16.8)</td>
</tr>
<tr>
<td>Presenting bAVM Rupture, n (%)</td>
<td>17 (100)</td>
<td>94 (88.7)</td>
<td>165 (89.9)</td>
<td>143 (88.8)</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-intervention Treatment</td>
<td>1 (5.9)</td>
<td>8 (7.6)</td>
<td>11 (5.9)</td>
<td>13 (8.1)</td>
</tr>
<tr>
<td>Microsurgery Only</td>
<td>15 (88.2)</td>
<td>80 (75.5)</td>
<td>131 (70.4)</td>
<td>118 (73.3)</td>
</tr>
<tr>
<td>Embolism Only</td>
<td>1 (5.9)</td>
<td>10 (4.4)</td>
<td>27 (14.5)</td>
<td>20 (12.4)</td>
</tr>
<tr>
<td>Radiosurgery Only</td>
<td>0 (0)</td>
<td>3 (2.8)</td>
<td>6 (3.2)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Microsurgery &amp; Embolism</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>4 (2.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Microsurgery &amp; Radiosurgery</td>
<td>0 (0)</td>
<td>2 (1.9)</td>
<td>3 (1.6)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Embolism &amp; Radiosurgery</td>
<td>0 (0)</td>
<td>2 (1.9)</td>
<td>4 (2.1)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>4 (23.5)</td>
<td>28 (26.4)</td>
<td>40 (21.5)</td>
<td>40 (24.8)</td>
</tr>
<tr>
<td>Parietal</td>
<td>0 (0)</td>
<td>22 (20.8)</td>
<td>43 (23.1)</td>
<td>32 (19.9)</td>
</tr>
<tr>
<td>Temporal</td>
<td>5 (29.4)</td>
<td>24 (22.6)</td>
<td>52 (28.0)</td>
<td>43 (26.7)</td>
</tr>
<tr>
<td>Occipital</td>
<td>3 (17.6)</td>
<td>15 (14.2)</td>
<td>30 (16.1)</td>
<td>27 (16.8)</td>
</tr>
<tr>
<td>Basal Ganglia &amp; Thalamus</td>
<td>0 (0)</td>
<td>7 (6.6)</td>
<td>15 (8.1)</td>
<td>9 (5.6)</td>
</tr>
<tr>
<td>Corpus Callosum &amp; Hippocampus</td>
<td>1 (5.9)</td>
<td>7 (6.6)</td>
<td>15 (8.1)</td>
<td>7 (4.3)</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>1 (5.9)</td>
<td>18 (17.0)</td>
<td>25 (13.4)</td>
<td>32 (19.9)</td>
</tr>
<tr>
<td>Brain Stem</td>
<td>0 (0)</td>
<td>3 (2.8)</td>
<td>3 (1.6)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Size, cm, mean (SD)</td>
<td>2.31 (1.16)</td>
<td>2.79 (1.40)</td>
<td>2.90 (1.50)</td>
<td>2.77 (1.43)</td>
</tr>
<tr>
<td>Hemodynamic Related Aneurysm, n (%)</td>
<td>3 (17.6)</td>
<td>22 (20.8)</td>
<td>29 (15.6)</td>
<td>40 (24.8)</td>
</tr>
<tr>
<td>Deep Venous Drainage, n (%)</td>
<td>7 (41.2)</td>
<td>42 (39.6)</td>
<td>76 (40.9)</td>
<td>72 (44.7)</td>
</tr>
<tr>
<td>Thick Drainage Vein or Venous Bulb, n (%)</td>
<td>3 (17.6)</td>
<td>42 (39.6)</td>
<td>70 (37.6)</td>
<td>65 (40.4)</td>
</tr>
<tr>
<td>Spetzler-Martin Grading, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (23.5)</td>
<td>16 (15.1)</td>
<td>27 (14.5)</td>
<td>27 (16.8)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>9 (52.9)</td>
<td>46 (43.4)</td>
<td>69 (37.1)</td>
<td>65 (40.4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (17.6)</td>
<td>28 (26.4)</td>
<td>55 (29.6)</td>
<td>44 (27.4)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (5.9)</td>
<td>14 (13.2)</td>
<td>28 (15.1)</td>
<td>21 (13.0)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0 (0)</td>
<td>2 (1.9)</td>
<td>7 (3.8)</td>
<td>4 (2.5)</td>
</tr>
</tbody>
</table>
Supplemental Table 2: Design and analysis of four scenarios on haemorrhage risk of brain arteriovenous malformation during risk and control periods in the Chinese population.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Included Individuals</th>
<th>Definition of Risk Period (Pregnancy)</th>
<th>Definition of Risk Period (Abortion)</th>
<th>Definition of Control Period</th>
<th>Risk Period</th>
<th>Control Period</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Attributable Risk Percent, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Haemorrhagic bAVM of all ages (n=311)</td>
<td>40-week gestation and 6-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting risk period</td>
<td>17 229 7.44% 305 8523 3.58% 2.078(1.275-3.387) 51.88</td>
<td>17 255 6.66% 305 8497 3.59% 1.855(1.138-3.023) 46.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td>17 236 7.20% 305 8516 3.58% 2.010(1.233-3.275) 50.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-week gestation and 12-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>17 263 6.47% 305 8489 3.59% 1.799(1.104-2.933) 44.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td>17 249 6.67% 305 8489 3.59% 1.799(1.104-2.933) 44.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Haemorrhagic bAVM of all ages with at least one previous pregnancy (n=161)</td>
<td>40-week gestation and 6-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting risk period</td>
<td>17 220 7.73% 151 6280 2.40% 3.214(1.946-5.306) 68.89</td>
<td>17 228 7.46% 151 6272 2.41% 3.097(1.876-5.113) 67.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td>17 247 8.88% 151 6253 2.41% 2.850(1.726-4.706) 64.91</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-week gestation and 12-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>17 265 6.67% 151 6245 2.42% 2.757(1.670-4.552) 63.73</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td>17 263 6.67% 151 6245 2.42% 2.757(1.670-4.552) 63.73</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Haemorrhagic bAVM of reproductive age (n=186)</td>
<td>40-week gestation and 6-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting both risk period and 15 yrs</td>
<td>17 126 13.48% 177 2133 8.30% 1.624(0.987-2.671) 38.42</td>
<td>17 140 12.11% 177 2119 8.35% 1.450(0.881-2.385) 31.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td>17 131 13.00% 177 2128 8.32% 1.563(0.950-2.571) 30.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-week gestation and 12-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>17 145 11.73% 177 2114 8.37% 1.401(0.852-2.304) 28.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td>17 145 11.73% 177 2114 8.37% 1.401(0.852-2.304) 28.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Haemorrhagic bAVM with at least one previous pregnancy of reproductive age (n=106)</td>
<td>40-week gestation and 6-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>Age at obliteration or last follow-up subtracting both risk period and 15 yrs</td>
<td>17 118 14.41% 94 1777 5.29% 2.723(1.625-4.565) 63.28</td>
<td>17 123 13.82% 94 1772 5.30% 2.605(1.554-4.367) 61.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td>17 132 12.88% 94 1763 5.33% 2.415(1.441-4.049) 58.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-week gestation and 12-week puerperium</td>
<td>6-week abortion and 6-week postabortion interval</td>
<td>17 137 12.41% 94 1758 5.35% 2.321(1.384-3.800) 56.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-week abortion and 6-week postabortion interval</td>
<td>17 137 12.41% 94 1758 5.35% 2.321(1.384-3.800) 56.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Supplemental Table 3: Search strategy of potentially related literature.

<table>
<thead>
<tr>
<th>Supplemental Table 3: Search strategy of potentially related literature.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pubmed</strong></td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
</tr>
<tr>
<td><strong>Web of Science</strong></td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
</tr>
<tr>
<td><strong>Step 4</strong></td>
</tr>
<tr>
<td><strong>Embase</strong></td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
</tr>
<tr>
<td><strong>CNKI</strong></td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
</tr>
<tr>
<td><strong>Wanfang</strong></td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
</tr>
</tbody>
</table>