Severe Secondary Postpartum Hemorrhage: A Historical Cohort

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ABSTRACT: Objectives: *The principal objective of our study was to describe the frequency of severe secondary postpartum hemorrhages (PPH). Our secondary objectives were to describe the different causes of PPH and to assess if the PPH etiologies varied by parity.* **Methods:** *This is a historical cohort study covering the period from January 1, 2004, through February 13, 2013, in a level III maternity ward. Women were eligible if they were treated for severe secondary PPH during their postpartum hospitalization or were admitted for it after discharge but before the 42nd day postpartum, regardless of the type of delivery. Women were excluded if they gave birth before 22 weeks of gestation or if they had experienced only an immediate PPH (≤ 24 hours after delivery). Eligible patients were identified by the hospital's administrative software. Primiparas and multiparas were compared with Student's* t *test and a chi-squared or Fisher's exact test.* **Results:** *The incidence of severe secondary PPH was 0.23 percent (*n *= 60/26,023). The mean time between delivery and PPH onset was 13.4 ± 10.8 days. The women's mean age was 30.4 ± 5.7 years and their mean body mass index was 23.4 ± 5.7 kg/m². Placental retention was the cause to which these hemorrhages were most frequently attributed (30.0%). Subinvolution of the placental bed was noted in 13.3 percent of the patients, endometritis in 10.0 percent, pseudoaneurysm of the uterine artery in 3.3 percent, and excessively strong resumption of menses in 3.3 percent; no cause could be determined for 16.7 percent of the cases. Neither clinical signs nor causes differed by parity.* **Conclusion:** *Secondary PPH is rare. Accurate diagnosis is based most often on histopathologic findings. (BIRTH 42:2 June 2015)*

Key words: *delivery, placenta, placental bed subinvolution, secondary postpartum hemorrhage*

Postpartum hemorrhage (PPH) remains one of the leading causes of maternal mortality and morbidity worldwide (1). Although immediate PPH (PPH ≥ 500 mL within 24 hours of delivery) has been studied repeatedly, these parameters are not true for secondary PPH; few studies have examined its frequency, causes, or medical and surgical management (2–5). Secondary PPH is defined as any significant bleeding from the genital tract, by any route (vaginal or intra-abdominal), from 24 hours after childbirth to the 42nd day postpartum (2–5).

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Some studies have considered only women for whom a histopathology examination was requested (4,6). The study with the largest number of participants (n = 243) was a case–control study intended to study the predictive factors of these secondary PPHs (5). The historical cohort studies are often old (2,3) or raise questions about the quality of the pathology examinations performed (3). No published European cohort study has assessed the frequency or causes of secondary PPH, and no scientific evidence supports any of the current treatment options (7). It is thus understandable that there are no guidelines for its management in France.

Depending on the study, the frequency of secondary PPH appears to vary from 0.2 to 3.0 percent of deliveries (2,3,8–10). This frequency is difficult to estimate because only severe secondary PPH results in readmission. Previous reports have been hospital-based studies that used data from maternity wards and thus considered only patients with PPH requiring surgical treatment or blood transfusion. The other patients were managed medically, on an outpatient basis, in hospital emergency departments, or by private practitioners. Moreover, the cause of the secondary hemorrhage often remains unknown, in the absence of routine uterine surgical evacuation, which is not always essential to the woman's medical care. It is, however, the histopathologic examination of these aspiration products that most often produces the diagnosis, especially that of subinvolution (also sometimes referred to as noninvolution or delayed involution) (2,3,8–11) of the placental bed (4,6,10,12). Subinvolution is an abnormal involution of the placental bed, characterized by widely distended and partly hyalinized maternal vessels.

In practice, clinicians lack adequate knowledge of the different causes of secondary PPH and focus mainly on the presence or absence of placental retention on ultrasound, without considering other possible causes (7,12). Fung et al have reported, however, that retained tissue was histologically confirmed in less than half of the women who underwent uterine evacuation for retained placental tissue (9).

The principal objective of our study was to assess the incidence of severe secondary PPH. Our secondary objectives were to describe the distribution of the different causes of severe secondary PPH and to assess whether it differed as a function of parity.

Method

Study Population

This historical cohort study covers the period from January 1, 2004, to February 13, 2013. We included all women who gave birth at the Clermont-Ferrand University Hospital Center (level III) and who had severe secondary PPH. In this study, severe secondary PPH has been defined as any significant bleeding from the genital tract, by any route (vaginal or intra-abdominal) from 24 hours after childbirth to the 42nd day postpartum, resulting in medical, interventional radiology, or a surgical procedure during the initial postpartum hospitalization or a subsequent hospitalization.

This study excluded all women who gave birth before 22 weeks (or to a fetus < 500 g), or who had only an immediate postpartum hemorrhage, that is, any significant bleeding by any route (vaginal or intra-abdominal), in the first 24 hours postpartum. We also excluded women with a secondary PPH at home who were not subsequently readmitted (i.e., who had only outpatient medical treatment and were not readmitted).

Study Design

The women were initially identified through the hospital discharge summaries, by looking for all women who were readmitted during the first 42 days postpartum or who had a medical, interventional radiology or surgical procedure during their postpartum hospitalization.

The medical data necessary for the study were obtained from the women's computerized medical records. These included notes and reports of all consultations, admissions, surgical procedures, and pathology examinations.

Statistical Analyses

The quantitative variables were compared with Student's t test and the qualitative variables with Pearson's chi-squared test (or Fisher's exact test, when appropriate). The value $p < 0.05$ was defined as significant. The data were analyzed with SAS software (SAS v 9.4; SAS Institute Inc., Cary, NC, USA).

Ethical Approval

The hospital has reported its computerized medical files to the National Data Protection Authority (CNIL), as required by statute. The data extracted for the study were entirely anonymized. The relevant ethics committee approved this study on November 25, 2013 (CECIC Rhône-Alpes-Auvergne, Grenoble, IRB 00005921).

Results

During the study period, there were 26,023 deliveries at the Clermont-Ferrand University Hospital Center level III maternity ward. We identified 60 patients with severe secondary PPH, for an incidence of 23 per 10,000 deliveries (0.23%). This incidence was 0.28 percent for vaginal deliveries and 0.08 percent for cesarean deliveries.

The women's mean age was 30.4 ± 5.7 years. Their mean body mass index was 23.4 ± 5.7 kg/m² and 52.0 percent of them lived with a partner (Table 1). Nearly one quarter (24.6%) smoked throughout their pregnancy. More than two thirds (67.3%) worked during pregnancy, and 7.7 percent were unemployed. Nearly all were French citizens (91.8%), although 15 percent were not born in metropolitan France. More than 16 percent had a previous cesarean delivery (Table 2).

The mean term at delivery for the births resulting in severe secondary PPH was 37.9 ± 2.6 weeks and 81.7 percent of the children were born after 37 weeks (Table 2). Vaginal deliveries accounted for 75 percent of the births (66.7% spontaneous and 8.3% operative), and cesareans 25 percent. After delivery, 19.0 percent of these women had an immediate PPH and 47.5 percent had soft-tissue injuries (Table 2). These injuries resulted from episiotomy in 32.1 percent of the patients and from perineal tears or lacerations in 46.4 percent, mainly second-degree tears (61.5%). The records reported no third- or fourth-degree perineal lacerations.

The mean time from delivery to the onset of the severe secondary PPH was 13.4 ± 10.8 days (range: 1–39 days). They occurred at home for 86.7 percent of the women. In more than half of the patients, the alarm signal was the onset of bright red vaginal bleeding. Clots of blood were observed in 47.3 percent. In our entire cohort, approximately 60.0 percent of the women had hyperthermia, and 50.0 percent had tachycardia. The physical examination revealed an abnormal uterine volume (23.2%), soft uterine consistency (17.9%), pain on abdominal palpation (24.6%), abdominal sensitivity (21.4%), pain on mobilization of the uterus (14.3%), or vulval anomalies (17.9%). In 27.6 percent of the patients, the woman had bleeding episodes during consultation. The uterus was the source of the bleeding for more than 90.0 percent of women.

Ultrasound was performed in 85.0 percent of the women and 78.4 percent of the abnormalities were identified, the most frequent of which was intrauterine placental retention (90.0%). The mean size of the intrauterine fragment identified was 43.9 ± 22.8 mm in height and 25.6 ± 17.8 mm in width. The rate of surgical treatment did not differ between women who had ultrasound (50.9%) and those who did not (49.0%) ($p > 0.05$). Magnetic resonance imaging with gadolinium injection was performed for three women (5.0%) and was helpful in the diagnosis of myometrial and uterine necrosis without effusion or abscess. Computed tomography (CT) with injection of a contrast product was performed in 11.7 percent ($n = 7$) of the patients. Findings were abnormal in four of these women (two patients with retention of an intrauterine clot, one hematoma of the anterior face of the uterus and bladder dome, and one pseudoaneurysm of the left uterine artery). The mean hemoglobin level at admission was 10.7 ± 2.4 g/dL. The initial diagnosis was placental retention in 60 percent of the women and endometritis in 15 percent (Table 3). Medical treatment was used for 86.7 percent of the women (Table 4), principally uterotonic agents (80.8%) and antibiotics (75.0%). Transfusion of packed red blood cells was necessary

Table 1. Women's social and demographic characteristics and medical history, Clermont–Ferrand University Hospital, France, 2004–2013

	Entire cohort N = *60* *(%) [mean±SD]*	*Primiparas* N = *30* *(%) [mean±SD]*	*Multiparas* N = *30* *(%) [mean±SD]*	P
Maternal age	[30.4 ± 5.7]	[30.0 ± 6.0]	[30.9 ± 5.6]	0.52
≥35 years	14/60 (23.3)	7/30 (23.3)	7/30 (23.3)	1.0
BMI	[23.4 ± 5.7]	[23.6 ± 5.7]	[23.5 ± 5.9]	0.43
>25	14/52 (26.9)	6/28 (21.4)	8/24 (33.3)	0.31
Tobacco*	14/57 (24.6)	5/29 (17.2)	9/28 (32.1)	0.20
Number of cigarettes	[7.5 ± 4.9]	[10.8 ± 5.5]	[5.4 ± 3.1]	0.08
Born outside metropolitan France‡	7/47 (14.9)	1/23 (4.4)	6/24 (25.0)	0.10
Work status	35/52 (67.3)	18/26 (69.2)	17/26 (65.4)	0.80
Number of pregnancies	[1.3 ± 1.7]	[0.4 ± 0.8]	[2.2 ± 1.9]	<0.0001
Previous cesarean†	10/60 (16.7)	0/30 (00.0)	10/30 (33.3)	-

**Smoked during pregnancy.* ‡*All geographic origins except metropolitan France (Africa, Asia, Europe, and overseas districts and territories).* †*Cesarean performed before the delivery preceding the episode of late postpartum hemorrhage. BMI=Body mass index.*

for 21.2 percent of the women, with a mean of 3.3 ± 0.9 units used. Surgical intrauterine evacuation was used in half of the patients for which intrauterine retention was suspected. Treatment for 15 percent of the women used arterial embolization, and its success rate was 100 percent. Only one woman required a total hysterectomy without salpingo-oophorectomy.

A histopathology examination was performed for 46.7 percent of the women with severe secondary PPH (n = 28) (Table 3). The examination showed placental retention in more than half of the patients, and subinvolution of the placental bed in approximately 29 percent.

Among the overall cohort, placental retention accounted for no more than 30.0 percent of the causes of severe secondary PPH; endometritis was found in 10.0 percent, and subinvolution of the placental bed in 13.3 percent, even though it was never mentioned as an initial diagnosis. In 16.7 percent of the patients, no cause of the severe secondary PPH could be identified (Table 3).

Social, demographic, and medical characteristics did not differ according to parity, except for the number of pregnancies (Table 1). The data about the delivery considered did not differ according to parity except for soft tissue injuries, which were more frequent in primiparas (60.0%) than in multiparas (34.5%) (p = 0.04) (Table 2).

The mean time until onset of severe secondary PPH did not differ according to parity (13.8 ± 11.4 days for the primiparas vs 13.2 ± 10.2 days for the multiparas). Ultrasound suggested placental retention in 89.4 percent of the primiparas and 90.4 percent of the multiparas (p = 0.79). Diagnosis at admission did not differ by parity (p = 0.77), nor did the pathology diagnosis, the final diagnosis (Table 3), or treatment (Table 4).

Discussion

The incidence of severe secondary PPH in our study was 23 per 10,000 deliveries (0.23%), consistent with the lowest incidence rate, reported by Boyd et al (8). Other studies have reported rates ranging from 0.4 to 1.4 percent (2,3,9,10,13,14). The principal cause of secondary PPH was placental retention (30%). Parity in our study did not influence the incidence of severe secondary PPH, and the distribution of its causes was the same in both primiparous and multiparous women.

The proportion of smokers in our study (24.6%) was similar to that reported by Mulic-Lutvica et al (26.3%) (15). On the other hand, the population studied by King et al included no women who smoked during pregnancy (3). The distribution of multiparas and primiparas was identical in our study, although another study reported a higher proportion of primiparas (15). The rate of spontaneous vaginal deliveries in our series

Table 2. Data about the delivery preceding the hemorrhage, Clermont–Ferrand University Hospital, France, 2004–2013

	Entire cohort N = *60* % *[mean±SD]*	*Primiparas* N = *30* % *[mean±SD]*	*Multiparas* N = *30* % *[mean±SD]*	P
Term at delivery (in weeks)	[37.9 ± 2.6]	[38.3 ± 2.9]	[37.6 ± 2.2]	0.34
Onset of labor				
Spontaneous labor	56.7	56.7	56.7	0.29
Induction of labor	23.3	30.0	16.7	
Cesarean	20.0	13.3	26.7	
Duration of labor (in hours)*	[4.6 ± 3.8]	[5.6 ± 3.9]	[3.5 ± 3.5]	0.05
Type of delivery				
Spontaneous vaginal	66.7	70.0	63.3	0.85
Operative vaginal	8.3	6.7	10.0	
Cesarean	25.0	23.3	26.7	
Natural placental delivery	15.1	14.3	16.0	1.0
Type of placental delivery				
Complete	88.3	93.3	83.3	0.42
Incomplete[‡] or complete placental reduction[†]	11.7	6.6	16.7	
Manual removal of the placenta	10.2	6.7	13.8	0.42
Immediate PPH	19.0	17.2	20.7	0.73
Perineal injuries	47.5[§]	60.0[¶]	34.5**	0.04

**Duration from 5 cm to full dilation. [†]Complete placental retention: 3.3% vs 0%. [‡]Incomplete placental retention after birth: 3.3% vs 16.7%. [§]Episiotomies: 32.1%; perineal tears or lacerations: 46.4%; other traumatic lesions: 21.4%. [¶]Episiotomies: 44.4%; perineal tears or lacerations: 38.9%; other traumatic lesions: 16.7%. **Episiotomies: 10.0%; perineal tears or lacerations: 60.0%; other traumatic lesions: 30.0%. PPH= Postpartum hemorrhage.*

Table 3. Diagnoses at admission, by histopathology, and at discharge, Clermont–Ferrand University Hospital, France, 2004–2013

	Entire cohort N= *60* %	*Primiparas* N=*30* %	*Multiparas* N= *30* %	P
Admission diagnosis*				
Placental retention	60.0	53.3	66.7	0.77
PPH endometritis with placental retention	3.3	3.3	3.3	
PPH endometritis without placental retention	11.7	16.7	6.7	
Excessively strong resumption of menses	5.0	6.7	3.3	
Other clinical diagnoses†	20.0	20.0	20.0	
Diagnosis by histopathology‡				
Placental retention	53.6	41.7	62.5	0.25
Subinvolution of the placental bed	28.6	25.0	31.3	
Other diagnoses§	17.9	33.3	6.2	
Discharge diagnosis¶				
Placental retention	30.0	23.3	36.7	0.37
PPH endometritis without placental retention	3.3	3.3	3.3	
PPH endometritis with placental retention	6.7	13.3	0.0	
Subinvolution of the placental bed	13.3	10.0	16.7	
Pseudo-aneurysm of the uterine artery	3.3	3.3	3.3	
Very excessive resumption of menses	3.3	3.3	3.3	
Other diagnoses**	23.3	30.0	16.7	
Not determined	16.7	13.3	20.0	

**Diagnosis selected by the clinician and noted in the medical file at admission. †Other clinical diagnoses: wound, hematoma, hemorrhage under anticoagulant treatment. ‡Diagnosis from pathology examination. §Other pathology diagnoses: necrotizing decidua, necrotic endometrium or myometrium, hemorrhagic material without placental tissue, necrotic, suppurated or pyometritic uterine tissue material. ¶Diagnosis based on all of the data available (medical, laboratory, and imaging). **Hematoma (4 cases), myometrial necrosis (4 cases), acquired (2 cases) or congenital (1 case), disorders of hemostasis, and diverse wounds (3 cases). PPH=Postpartum hemorrhage.*

Table 4. Medical and surgical management of secondary hemorrhages, Clermont–Ferrand University Hospital, France, 2004–2013

	Entire cohort N=60 % [mean±SD]	*Primiparas N=30 % [mean±SD]*	*Multiparas N=30 % [mean±SD]*	*P*
Medical treatment	86.7	90.0	83.3	0.35
Uterotonic agents	80.8*	70.4†	92.0‡	0.08
Antibiotic therapy	75.0	81.5	68.0	0.26
Blood transfusion	21.2	22.2	20.0	0.84
Red blood cells units	[3.3 ± 0.9]	[3.6 ± 1.0]	[2.8 ± 0.5]	0.15
Fresh frozen plasma	11.5	18.5	4.0	0.19
Surgical treatment				
Intrauterine evacuation	50.0	50.0	50.0	1.0
Other surgery	1.7	3.3	0.0	
Vascular embolization	15.0	13.3	16.7	1.0

**Oxytocins: 83.3%, prostaglandin: 4.8%, combination of oxytocins and prostaglandin: 11.9%. †Oxytocins: 78.9%, prostaglandin: 5.3%, combination of oxytocins and prostaglandin: 15.8%. ‡Oxytocins: 87.0%, prostaglandin: 4.4%, combination of oxytocins and prostaglandin: 8.7%.*

was similar to that reported in one previous publication (3), but was globally lower than the rates in other studies (15,16). The rate of operative vaginal delivery in our study was similar to that in the study by Feigenberg et al (16), but was much lower than that in King et al (3). We observed twice as many cesareans and eight times more soft-tissue injuries (such as episiotomy) than the latter did (3). The global rate of cesarean

delivery in our maternity ward was 24.8 percent in 2004 and 18.5 percent in 2013, and the global rate of episiotomy was 25.1 percent in 2004 and 23.7 percent in 2013 (17). The global cesarean rate in France was 19.0 percent in 2004 and 18.8 percent in 2010, and the global episiotomy rate was 41.1 percent in 2004 and 28.5 percent in 2010 (18). The proportion of primary PPH among women with secondary PPH in our study (19%) corresponded to that reported by other authors (between 7.23 and 31.6%) (3,16,19), but it was higher than in our global population (around 7.1% in 2013). It has been suggested that immediate PPH is a predictive factor of secondary PPH (10).

Similarly, the mean interval between delivery and onset of the secondary PPH was 13.4 ± 10.8 days, not very different from previous studies. The interval ranged from 7 to 14 days for most studies (2,13). Pelage et al found a mean of 16.3 ± 11.6 days (20).

Ultrasound is generally considered to help diagnosis by identifying the material retained in the uterus. It is nonetheless difficult to interpret because the presence of intrauterine material does not necessarily involve intrauterine retention of placental tissue. That is, a uterine cavity containing an organized blood clot produces heterogeneous ultrasound images similar to those suggesting placental retention (13). Use of ultrasound was frequent (85.0%) in our series because of the availability of ultrasound in our maternity ward, compared with other studies (10). This result is surprising, because all gynecologic emergencies generally undergo ultrasound. We did not, however, find any trace of an ultrasound in some files. Hoveyda et al reported in 2001 that uterine evacuation was more frequent for women who underwent ultrasound screening than for those who did not (10). Nonetheless, use of ultrasound did not influence the rate of surgical intervention in our study ($p > 0.05$) and our rate is similar to that of a previous study with fewer ultrasounds (10). The diagnoses mentioned in our study after the ultrasound were similar to those reported by other authors (2,10). Some authors have suggested that the sensitivity and positive predictive value of this examination could be improved by performing it earlier (13) or by adding a Doppler of the intrauterine mass and/or the uterine artery (15,19). A resistance index below the 10th percentile and the absence of a protodiastolic notch are frequently found in women with placental retention (15). Ultrasound images showing an echogenic intrauterine mass with a uterine measurement above the 90th percentile may also be associated with placental retention (19).

In short, only histologic examination of the uterine contents can confirm the placental nature of the intrauterine material or provide certainty about subinvolution of the placental bed. Our confirmation rate for placental retention was 53.6 percent, well above the 32.0 percent rate (29/89) reported in 1966 in an English study of secondary PPH (2). Subinvolution of the placental bed is a nosological entity that has been the cause of secondary PPH since 1945 (21). On tissue examination, we found empty placental uterine vessels without any vitelline tissue. Histological examination of the tissue after normal involution of the placental bed on one hand revealed a proliferation of the intimal layer, which reduced the vascular lumen; on the other hand, regeneration of the internal elastic strips and hyalinization of the tunica media resulted in vascular occlusion (11,22). When involution of the placental bed is delayed, the uteroplacental vessels have no endothelial layer, which may explain the presence of thrombotic material partially blocking the vessel lumina (6). Histologically, large superficial myometrial vessels are observed, dilated with hyaline material that replaces the medial layer and endovascular thrombi of different ages (10). This cause is not well known by gynecologists, which may explain why it was never mentioned as an initial diagnosis in our study. The incidence of this cause in our study is higher than that reported by Khong et al (17.7%) (4). Subinvolution of the placental bed can be associated with placental retention, as reported in an Australian study that found subinvolution in 20 of the 23 deliveries of placental retention that included maternal vessels in the curettage material (4). Subinvolution of the placental bed has also been described for molar pregnancies (23).

The literature reported variable proportions of medical treatment, often rates higher than in our department (2). Although the use of uterotonic agents in our study was less regular than in some other studies (2,15,24), we nonetheless used them more frequently than Hoveyda et al (43.2%) (10). Our use of antibiotic treatment (78.6%) was similar to that in the study by Pelage et al (24), but less frequent than that of other authors (92.0–97.0% of patients) (3,10). On the other hand, the rate of prophylactic antibiotic treatment in our study (2) was close to that reported by Mulic-Lutvica et al (40.0%) (15). The rate of transfusion of packed red blood cells observed in our study was similar to rates in earlier studies (10.0–30.0%) (2,13,15).

In some patients, medical intervention made it possible to stop the secondary hemorrhage. In many patients, techniques to evacuate the uterus were necessary. Authors have reported rates of surgical uterine evacuation ranging from 34.8 to 91.7 percent (2,8,10,24); these rates are higher than ours. It would be reasonable as a first-line treatment to use medical treatment initially, reserving surgical management for patients when the first treatment fails (10,19). We observed no complications associated with uterine evacuation, although other studies have reported patients with uterine perforation (10,16). Appropriate

management is not well codified. Our success rate for embolization among women with a severe secondary PPH (15%) was identical to that of Pelage et al (24). Embolization makes it possible to avoid hysterectomy, while theoretically preserving the possibility of another pregnancy. In our study, it was observed that only one woman required a hysterectomy, suggesting that this finding is a rare complication of secondary PPH.

The identification of secondary PPH in our historical cohort was retrospective, based on administrative data, and women with secondary PPH after discharge who were not readmitted were not included in our study; it thus underestimates the incidence of secondary PPH, but our aim was to estimate severe secondary PPH. Recruitment bias is also possible because the women who previously had an immediate or a secondary PPH might be more likely to choose a level III facility for their next delivery. It is also possible that patients who have undergone a cesarean delivery are more likely to be readmitted because of surgical complications and might therefore be more likely to have a secondary PPH diagnosed as they are being monitored in the hospital.

Conclusion

In conclusion, secondary PPH is a rare complication but one that can result in severe maternal morbidity. Its management is not well codified in the absence of population-based studies including an adequate number of individuals; its clinical and ultrasound features most often suggest placental retention to clinicians. Ultrasound does not enable the specific cause of secondary PPH to be identified, unlike a pathology examination, which is the only means of identifying subinvolution of the placental bed. Parity does not seem to have an influence on severe secondary PPH substantially, and its causes did not differ according to parity. It would be useful to conduct a population-based prospective cohort study to verify the incidence of secondary PPH and to assess its predictive factors. Thus women having risks of secondary PPH would receive individual risk-based counseling before their hospital discharge.

Conflict of Interests

The authors declare no conflicts of interest and there has been no significant financial support for this work that could have influenced its outcome.

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