Aneurysmal Subarachnoid Haemorrhage in Pregnancy - review and pooled data analysis

Chiara Robba [1], Susanna Bacigaluppi[2], Nicola Luigi Bragazzi[3], Federico Bilotta[4], Mypinder S Sekhon[5], Rita Bertuetti[1], Ari Ercole[1], Alessandro Bertuccio[7], Marek Czosnyka[8], and Basil Matta[1]

[1]Neurosciences Critical Care Unit, Cambridge University Hospitals NHS Foundation Trust, UK.
[2]Department of Neurosurgery, Galliera Hospital, University of Genoa, Italy
[3]Department of Health Sciences (DISSAL), University of Genoa, Italy
[4]Department of Anaesthesiology, University of Rome "La Sapienza", Rome, Italy
[5]Department of Medicine, Division of Critical Care Medicine,Vancouver General Hospital, Canada.
[7]Department of Neurosurgery, S.George's Hospital, University of London, United Kingdom.
[8] Division of Neurosurgery, Brain Physics Laboratory, Addenbrooke's Hospital, University of Cambridge, United Kingdom

Corresponding Author:

Dr. Chiara Robba, M.D.

Neurosciences Critical Care Unit, Box 1, Addenbrooke's Hospital, Hills Road, Cambridge, UK CB2 0QQ

Mail: kiarobba@gmail.com

Phone +39 3473912338

Chiara Robba, MD: Department of Neurosciences, Addenbrooke's Hospital, Cambridge University, Box 1, Addenbrooke's Hospital, Cambridge University Hospitals Trust, Hills Road, Cambridge, CB2 0QQ. Email: kiarobba@gmail.com

Susanna Bacigaluppi, MD, PhD: Department of Neurosurgery, Galliera Hospital, Mura delle Cappuccine 16, 16128 Genova . Email:susannabacigaluppi@yahoo.it

Nicola Luigi Bragazzi,MD, PhD: Department of Health Sciences (DISSAL), Saint Martino Hospital, Largo Rosanna Benzi 15, 16100 University of Genoa, Italy.Email: nicolabragazzi@gmail.com

Federico Bilotta, MD, PhD, Department of Anesthesiology, University of Rome "La Sapienza", Rome, Italy. Email: bilotta@tiscali.it

Mypinder S Sekhon,MD: Department of Medicine, Division of Critical Care Medicine, Vancouver General Hospital, West 12th Avenue, University of British Columbia, Vancouver, BC, Canada, V5Z 1M9. Email: mypindersekhon@gmail.com

Rita Bertuetti,MD: Department of Neurosciences, Addenbrooke's Hospital, Cambridge University, Box 1, Addenbrooke's Hospital, Cambridge University Hospitals Trust, Hills Road, Cambridge, CB2 0QQ. Email: rita.zoso82@gmail.com

Alessandro Bertuccio, MD: Department of Neurosurgery, S. George's Hospital Blackshaw road Tooting

SW170QT London.Email: aleberto@gmail.com

Ari Ercole,PhD, FRCA: Department of Neurosciences, Addenbrooke's Hospital, Cambridge University, Box 1, Addenbrooke's Hospital, Cambridge University Hospitals Trust, Hills Road, Cambridge, CB2 0QQ. Email: ae105@cam.ac.uk

Marek Czosnyka, MD, PhD: Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital, University of Cambridge, Hills Road, Cambridge, CB2 0QQ . Email: mc141@medschl.cam.ac.uk

Basil Matta,MD: Department of Neurosciences, Addenbrooke's Hospital, Cambridge University, Box 1, Addenbrooke's Hospital, Cambridge University Hospitals Trust, Hills Road, Cambridge, CB2 0QQ.Email: bmatta@addenbrookes.nhs.uk

Abbreviations list

ACA Anterior Cerebral Artery
AcomA Anterior Communicating Artery
AGF Angiography
aSAH aneurysmal subarachnoid haemorrage
BA Basilar Artery
CI Confidence Interval
COPD chronic obstructive broncopulmonary disease
CS Caesarean Section
CSF Cerebrospinal Fluid
CT Computed Tomography
CTA Computed Tomographic Angiography
DSA Digital Subtraction Angiography
GCS Glasgow Coma Scale
GOS Glasgow outcome Score
ICA Internal Carotid Artery
MCA Middle Cerebral Artery
MRA Magnetic Resonance Angiography
MRI Magnetic Resonance Imaging
NA Not Available
NCCU Neurosciences Critical Care Unit
NIS Nationwide Inpatient Sample
PCA Posterior Cerebral Artery
PcomA Posterior Communicating Artery
PICA Posterior Inferior Cerebellar Artery
SD Standard Deviation
SIADH Syndrome of inappropriate antidiuretic hormone section
VA Vertebral Artery

Abstract:

Background: Aneurysmal subarachnoid haemorrhage (aSAH) during pregnancy represents an important cause of maternal and foetal morbidity and mortality. Approaches to diagnostics and treatment are still controversial and there are only a limited number of cases described in the literature. Our study examines the management of aSAH in pregnant patients creating a case series by combining patients from our hospital records with those from the limited available literature.

Methods: Cases published between January 1995 and January 2015 were studied. Chi-squared test, exact Fisher's test, and chi-squared test for trend were used for analyzing categorical data, whilst t-test and U Wilcoxon-Mann-Whitney test for continuous data.

Results: 52 patients were included. The mean age was 31.47±5.80 and most patients were in their third trimester. A univariate pooled data analysis suggested that the maternal outcome may depend on mother's age, mother's Hunt and Hess score and Glasgow Coma Scale at arrival, treatment modality for the aneurysm, mode and timing of delivery. However, at the multivariate analysis only the presence of general complications resulted to significantly impact on maternal outcome.

Conclusions: Ruptured aneurysms in pregnant patients with aSAH may be safely secured in a timely manner. The diagnostic and treatment strategy for each of these patients should consider peculiar maternal and obstetric factors and requires a multidisciplinary assessment involving obstetrics, neurosurgeons and intensivists. Considering the observed statistical power of our series, our findings should be taken with caution and should be supported by further systematic data collection.

Keywords: pregnancy; subarachnoid haemorrhage; delivery; cerebral aneurysm.

Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) during pregnancy is an uncommon event, affecting only between 0.01 and 0.058% of pregnant women [11, 39]. As a result, published literature on the management and outcome is limited. However, it is the third leading cause of maternal death from non-obstetric causes, accounting for 5% to 12% of total mortality during pregnancy and it is associated with serious morbidity of both mother and foetus [11]. Several para-physiological changes occur in the human body during pregnancy, such as hormonal and hemodynamic changes including alterations to blood pressure and increased plasma volumes [53]. Hormones (oestrogen, progesterone, human chorionic gonadotropin) can lead to a remodelling of the arterial and venous intima and media [48]. Such structural changes of the arterial wall are mechanisms implicated in aneurysm formation and rupture [2]. However, the pathophysiology of aSAH is more complex and poorly understood. The role of sex hormones is far from clear. Oestrogen has been shown to confer some protection from aSAH [18, 34, 52]. At the same time, evidence from epidemiological studies of the prevalence of SAH in women and men or in women taking hormone replacement therapy (HRT) is not clear cut [38], and it has not been conclusively demonstrated that aneurysm rupture is more frequent in pregnancy.

The risk of rebleeding after aSAH is greatest in the first 2 to 12 hours and has an incidence in the range of 4-13.6% within the first 24 hours, rising up to 10–20% in the first month [4, 43]. As a consequence, it is generally accepted that ruptured aneurysms should be secured as early as possible [45, 53]. The mortality from aSAH in pregnant untreated patients is twice as high as in treated patients (10.2% *versus* 5.2%[26]). Thus, treatment principles for pregnant patients with ruptured intracranial aneurysms should not differ from those applied to non-pregnant patients.

Diagnostic and management strategies are complicated by maternal-foetal considerations: there is an understandable clinical anxiety in pursuing invasive interventions in pregnant patients. Furthermore, inclusion of these patients into randomized research studies is of ethical concern and there is a paucity of high-quality literature regarding the optimal management and outcomes of gravid patients with

concomitant neurological critical illness.

In this manuscript we pool published case reports and series in the literature with data from our retrospective analysis of obstetric patients admitted for aSAH to our tertiary specialist neurosciences critical care unit. Our aim is to create a series of sufficient number to characterize the presentation of aSAH in pregnancy, and to synthesize an overview of contemporary management strategies and outcomes of this rare but nevertheless important disease.

Methods

Data collection

Using routinely collected registry data, we obtained a list of gravid and peripartum patients (within three weeks of delivery) admitted to our Neurocritical Care Unit between 1st January 2000 and 1st January 2015. Our series was complemented by an extensive literature review performed by searching PubMed/MEDLINE including references between January 1995 and January 2015 using the search terms 'pregnancy', 'subarachnoid haemorrhage', and 'ruptured intracranial aneurysm' with wild-card options and Medical Subject Headings (MeSH) terms where appropriate. Only English language articles were included. All published case reports and case series on pregnancy related aSAH were considered relevant and selected for review. Additional material was obtained from the reference list of selected articles. Review articles were not retained in our analysis but bibliographies were scanned to increase the yield of potentially relevant manuscripts.

Statistical analysis

Data were checked for deviation from normal distribution (D'Agostino and Pearson omnibus normality test) and homogeneity of variance. Chi-square, exact Fisher, and chi-square test for trend were used for analyzing categorical data, whilst *t*-test, *t*-test with Welch's correction (in case of unequal variance) and Wilcoxon-Mann-Whitney U tests (in case of violation of normal distribution) for continuous data. Prognostic variables are tabulated both as raw and as adjusted, after adjusting for confounding variables (demographic variables). When performing multivariate analysis, also F-statistics, overall

fitting R^2 (raw and adjusted), partial η^2 and observed statistical power were computed. Analysis was carried out with MedCalc® (Version 15.8, MedCalc software bvba) and SPSS version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). For all the analyses a 5% significance level was set.

Results

A total of 22 papers reporting aSAH in pregnancy were found, constituting data from a total of 45 patients. Reports ranged from single cases (13 papers) to a maximum of seven cases (one case included in [50] had an unruptured aneurysm) (Table 2). Study details are shown in tables 1 and 2, whilst the results of our pooled analysis are tabulated in table 3 and 4. In one study that describes 8 patients with spontaneous SAH in pregnancy, only 1 case was presented with adequate details to be included in this case series [47].

Cumulative results:

Within this cumulative series 52 cases of pregnant patients affected by aSAH, mean age was 31.5±5.8 (range 20-42; median 31). 73.1% of patients (*n*=38) were in their third trimester, 19.2% (*n*=10) in their second and 7.7% (*n*=4) in the first trimester. More specifically, the mean gestation was 29.0±8.10 (9-39; 32); three cases were not specified, one case occurred was during labour [20], another case was one hour after CS and the third case on day 12 postpartum [5]. The presence (61.9%, *n*=13) or absence (38.10%, *n*=8) of risk factors was reported in 21 cases. Hypertension was the most common risk factor (affecting six patients, 30% of our cumulative series), followed by older age (3 patients were older than 40 years), and finally by alcohol and cigarette abuse (two cases). Chronic obstructive pulmonary disease, gestational diabetes, and familiarity for ruptured aneurysm were present in just one patient. Two patients had a history of previously complicated pregnancy by preeclampsia and one by eclampsia.

Headache was the most frequent presenting symptom in our cumulative series, affecting 79.6% of the patients (nearly all the non-comatose patients). Signs which might be associated with intracranial hypertension (confusion, vomiting, neurological deterioration) were seen in half of SAH patients (53%); 14.3% presented with focal signs, and seizures were present in 14.2% cases. Seizures were the only sign at presentation of two patients. Two cases presented with cardiogenic shock, and for three cases symptoms at presentation were not reported.

Mean GCS at presentation (not available in one case) was 12.8±3.9 (3-15; 15). Mean Hunt and Hess score (8 cases not available) was 2.7±0.9 (2-5; 2). Fisher score was described for 67.3% (n=35) patients. Of these cases, 65.7% (n=23) presented a Fisher Score IV, and 34.3% (n=12) with Fisher score between I and III. Moreover, CSF diversion was reported in 5 patients (see Table 2).

Including the Posterior Communicating Artery (PcomA) aneurysms (7 cases) within the anterior circulation aneurysms, the distribution of the aneurysms was in the 76.9% of the patients in the anterior circulation (n=15 Internal Carotid Artery or ICA, n=9 Middle Cerebral Artery or MCA, *n*=6 Anterior Communicating Artery or AcomA, *n*=2 Anterior Cerebral Artery or ACA, *n*=7 PcomA) and 23.0% in the posterior circulation (*n*=8 Vertebral Artery or VA, Basilar Artery or BA, Posterior Inferior Cerebellar Artery or PICA and *n*=4 Posterior Cerebral Artery or PCA). In one case the patient had multiple aneurysms and the site of the ruptured is not specified; it was likely to have involved the anterior circulation [5]. In terms of diagnostic procedure (5 cases are not specified), CT followed by CT-angiography (CTA) or digital subtraction angiography (DSA) was used in 9 and 31 cases respectively. Only in three cases did diagnosis and treatment avoid ionizing radiation entirely (MRI followed by MR angiography (MRA) and aneurysm clipping). In one case [46] CS was performed after diagnostic MRA and DSA was acquired thereafter.

Aneurysm occlusion was achieved by surgical clipping in 53.8% of the cases (*n*=28), and with an endovascular procedure in 36.5% (*n*=19). 9.6% (*n*=5) did not receive any treatment; in one of these, the aneurysm thrombosed spontaneously and in three cases no treatment was possible due to the critical condition of the mothers. Timing of delivery with respect to treatment to secure the aneurysm

was available in 49 of 52 cases: At term in 14.3% (*n*=7) and after treatment in 30.6% (*n*=15), before treatment in 24.5% (*n*=12), and at the same time as treatment in 22.4% (*n*=11). One foetus was aborted after endovascular treatment at the eleventh week of pregnancy, and 2 foetuses died *in utero* as a consequence of the death of their mothers. One patient (2.0%) did not require any treatment.

Data on the mode of delivery was available for 49 out of 52 women; three women (6.4%) did not deliver at all (one abortion and two deaths *in utero*). Of the remaining 46 patients, 72.3% (*n*=34) had a CS, of which more than 70% were emergency procedures. The remaining 25.5% (*n*=12) had a vaginal delivery. Vasospasm / delayed cerebral ischaemia was reported in 9 cases, being present in 8 patients (88.9%) and absent in 1 patient (11.1%). Other general / non-specific complications were reported in 16 cases (32.6%): SIADH (one case), infective complications (3 cases), cardiopulmonary complications (3 cases), cerebral oedema (3 cases), and rebleeding (2 cases). 33 patients (67.3%) did not report any general complications.

Mean maternal GOS was 4.2±1.37 (1-5; median 5). A good outcome of the mother (GOS=4 or 5) at discharge was observed in 84.6% (*n*=44 cases). Six women died during hospitalization and one died seven days after discharge making a total of 14% mortality. Two patients had a GOS of 3. Hunt-Hess score at admission (1-3 versus 4-5) strongly correlated with GOS (4-5 versus 1-3) (X^2 test; *p*=0,0019), whereas the Fisher Score (1-3 versus 4) did not (X^2 test; *p*=0,38). No association between the mode of delivery and the mother's GOS (X^2 test; *p*=1) was found.

Outcome of the babies was available for 44 out of the 54 cases (two twins). 84.1% (*n*=37) of the babies had a good condition at birth (defined with Apgar score ≥4). Seven (15.9%) had a low Apgar score (between 1 and 3); two babies died *in utero*; two immediately after birth, one pregnancy was terminated, making a total of 5 deaths (11.4%). The outcome of the baby seemed to depend on mode (*p* <0.001) and timing (*p* <0.001) of delivery, Hunt and Hess score (*p*=0.014) and GCS at arrival (*p*=0.047) (see Table 2). Statistical findings from pooled data analysis with respect to maternal and baby outcome are shown in table 3. Treatment modality, timing and mode of delivery, Hunt and Hess Grade, GCS, general complications, trimester of presentation and maternal age were found to be

significantly correlated with maternal outcome. Treatment modality, timing and mode of delivery, Hunt-Hess Grade and GCS were found to be statistically correlated with fetal outcome.

In contrast to the above univariate results, in a multivariable model (Table 4) only general complications were found to have a statistically significant impact on maternal outcome. In particular, the presence of general / non-specific complications is characterized by an odds-ratio (OR) of 1.45 [95% CI 1.16-1.82] of having a poor outcome. No variable resulted to have an influence on baby outcome.

Discussion

This case series of clinical data from gravid and peri-partum patients with aSAH – extracted from a retrospective analysis of internal cases and from published literature – aims to present the largest available picture of this unique group of patients.

The mean age of this cumulative series described is similar to that reported by a Nationwide Inpatient Sample (NIS) (30.3±8.0) [26], and it is much lower than the average age of female aSAH in general [6]. According to this database (NIS), the prevalence of unruptured aneurysms among all women of pregnancy age is 1.8%. Kim *et al.* [26] suggested that the risk of aneurysm rupture during pregnancy is not increased as compared to the general population of the same age and sex (1.4%; 95% CI = [1.35-1.57]). However, an increase in risk of rupture seems towards the third trimester with a peak during labour and delivery [57], and our results support this. Indeed, 73% of the patients of our cumulative series presented in the third trimester of pregnancy or peripartum (defined as within 3 weeks from delivery).

Risk factors and presentation in pregnant aSAH patients are similar to those commonly reported for aSAH patients in general. However, a history of hypertension is present in two thirds of aSAH patients in general [33] and yet it features in just 10-20% of aSAH cases in pregnancy [36]. Tobacco smoking [23] is described in half of aSAH patients [33]. Less common risk factors are hypercholesterolemia, alcohol abuse and diabetes mellitus [33], which are also present in pregnant patients. In addition,

eclampsia is involved in 14–40% cases of intracranial haemorrhages and risk increases in the postpartum period [28].

Headache is the most common symptom at presentation [12] and can be associated with nausea and vomiting as well [15] or with signs of meningism such as neck stiffness, affecting up to 90% of the patients (reviewed in [53]). In the general aSAH population, seizures occur at presentation in 3 - 21% of cases [10], similarly to our cumulative series of pregnant aSAH patients. Focal neurological signs were less common in our series than the literature reports for pregnant aSAH patients (14,3% vs. 30%) [53].

Radiation protection is of particular concern for both the diagnosis and the choice of treatment strategy because of the risks of radiation exposure to the foetus. The traditional preoperative assessment for aSAH patients in general, typically includes CT followed by CTA, DSA or less frequently by MRA [27]. Whereas a head CT scan involves an exposure of 1.1-2.5mSv, a CTA typically involves 3.57-5.73 mSv and 2-dimensional DSA has an even higher radiation burden of around 10.5 mSv [1]. However, these are whole body doses and do not necessarily reflect the dose to the foetus. Indeed, some studies have concluded that the risks for the foetus associated with CT are very low [55]. Some authors have argued that magnetic resonance imaging (MRI) is to be preferred [29]. However, MRI is less ubiquitously available and scanning times are much longer than with CT and so agitated patients may require sedation. Therefore, for most of the cases that we present, a CT followed by CTA or DSA was performed for the diagnosis. In one case ([46], case 1), MRA confirmed a ICA aneurysm, and endovascular coiling with DSA was performed after emergency CS to avoid the risk of foetal exposure to radiations. Even for treatment, the endovascular procedure is associated with a radiation dose to the foetus of 4.9 mSv, considered below the teratogenic dose [35].

The choice of the aneurysm treatment method is very controversial. According to the International Subarachnoid Aneurysm Trial (ISAT) [40], most of the aneurysms (97.3%) are located in the anterior circulation; our revised series similarly showed a clear-cut prevalence of aneurysms for that region (75%). In our review anterior or posterior circulation aneurysm location did not seem to associate with

a specific choice of treatment modality (clipping or coiling). This confirms that indications for either clipping or coiling are not clear-cut since in most cases both are regarded as technically feasible [7]. Aneurysm location did not seem to relate to clinical (Hunt Hess score; Welch's *t*-test *p*-value=0.059, statistically borderline) or radiological grade (Fisher grade) at admission. However, in the present series, all treated BA aneurysms were coiled in line with the current trend in practice [7]. In general, local experience is probably most important in determining treatment modality [7].

We did not see any relationship between clinical (Hunt-Hess score) or radiological grade (Fisher grade) at admission and choice of treatment modality employed. Reports are controversial [32] regarding the choice of treatment modality in relation to clinical grade, but other authors also observed that clinical outcomes seem not to differ between clipped or coiled patients [30, 51].

The utility of surgery for Fisher grade IV patients in prevention of complications of vasospasm and need of permanent ventricular shunt is not appraised by all authors [21, 56], though several studies are in favour of its efficacy [60, 61]. In this cumulative series, coiling or clipping are not even influenced by the trimester of pregnancy at presentation. However, clipping should be performed when delivery is not possible before treatment to avoid the foetal risks associated with endovascular treatment (prolonged radiation exposure, the need for systemic anticoagulation, the risk for incomplete aneurysm exclusion or post procedural rupture) [30]. Moreover, the angiography suite can be a hazardous environment in the event of foetal distress, with limited monitoring or equipment to facilitate a potential precipitous delivery [35]. Kim et al. [26] do not provide any information about timing of delivery in respect to treatment of the aneurysm. Nevertheless, the increasing trend [29, 37, 46] towards the use of coiling in pregnancy, as in our review, is likely to be motivated by both ISAT studies [40, 41].

Another important consideration is the mode and timing of delivery. This decision requires a multidisciplinary discussion that should involve neurosurgeons, intensivists, obstetricians, neonatologists and anaesthetists, and should take into consideration the condition of both the mother and of the foetus. Although there are no expert guidelines concerning the obstetric management of

pregnant patients affected by aSAH, emergency CS should be considered when the clinical state of the mother is life-threatening (coma, brainstem damage), if the interval between the treatment of the aneurysm and labour is likely to be less than 8 days, and if the diagnosis of the aneurysm is in a late stage of pregnancy [42]. In particular, for gestational ages beyond 34 weeks (reviewed in [53]) an emergency CS should be considered. By contrast, in the early stages of pregnancy (and in particular before the 24th gestational week) the expected survival rate for the foetus is very low and the patient should be treated essentially as if not pregnant [22, 31, 46].

Between the 24th and 34th week, each case should be considered and evaluated according to the conditions of the mother and of the foetus following a multidisciplinary discussion. We found that decisions regarding the timing of delivery with respect to aneurysm treatment was not influenced by the clinical conditions of the mother at presentation or by neuroradiological findings (Fisher score), instead only depending on the trimester of aSAH presentation. Thus, women who present with aSAH in the first and second trimester are usually treated like non-pregnant patients, undergoing treatment of the aneurysm before continuing their pregnancy at term. Patients who present symptoms in their third trimester show an increased rate of delivery previous to aneurysm treatment.

Once the aneurysm is secured, pregnancy can be allowed to progress to term. Since delivery mode could have an impact on maternal outcome, the decision for the delivery option should be based on clinical (neurological, obstetric) indications. Indeed in our cohort, the mode of delivery had no significant correlation with the trimester of aSAH presentation and did not influence outcome. Although in principle there is no neurosurgical contraindication to vaginal delivery following aneurysm occlusion [11], CS might be preferable under some circumstances such as if labour is likely to occur shortly after treatment of the aneurysm, or if there is an incomplete occlusion of the aneurysm [40].

The choice for timing of delivery also strongly depends on the choice of treatment modality for the aneurysm. Clipping is usually performed before or at the same time as CS. Once the baby has been delivered, both endovascular or surgical treatment are options as with any other aSAH patient.

Moreover, according to our analysis (table 3), mothers who delivered after or at the same time as aneurysm treatment had a better outcome.

Vasospasm/delayed cerebral ischemia was reported for only 15% cases in our series. This percentage represents a lower incidence compared to general literature that suggests symptomatic vasospasm occurs in about 30% of aSAH patients [62]. This complication may be likely underestimated/under-reported by several authors, or perhaps there could be some protective factors in pregnancy (such as haemodilution and hypervolemia) [6]. Of those patients that survived vasospasm, all had a good outcome at discharge. Fatal complications were cardiopulmonary arrest [25] and cerebral oedema [50], however all these four cases had GCS 3 at presentation and thus were already in severe conditions at arrival.

Our results show that most of the patients fully recovered and had no significant neurological deficits at discharge, with GOS score in the range 4-5 (83%). As expected, GOS was strongly linked to clinical condition at presentation (Hunt-Hess score) [19, 24]. Three of our revised cases presenting with cardiogenic shock and/or coma and thus with a very severe Hunt-Hess score and low GCS [5, 25, 50] died. This, again, confirms data from the literature claiming that conditions at arrival are prognostic for short-term outcomes [16, 19, 24].

Aneurysmal SAH in general is characterized by a high mortality rate in the acute phase between 8 and 67% [44]. In our review one mother in every ten with aSAH died, and this confirms that mortality from aSAH in pregnancy is still remarkable (9.5% [26]), ranging from 13 to 85% (reviewed in [53]).

Even though most of the babies had a good outcome, foetal mortality is still appreciable. All the 4 cases of death *in utero* were the consequence of maternal death, and independent from mode of delivery. In one case the foetus was aborted after endovascular treatment of the aneurysm, though information on the indications were not available.

In summary, our univariate pooled data analysis (table 3) showed that the maternal outcome may be related to the mother's age, mother's Hunt-Hess score and GCS at arrival, treatment method for

securing the aneurysm, mode and timing of delivery. The foetal outcome may be determined by maternal neurological status at arrival (Hunt-Hess score and GCS), as well as mode and timing of delivery. However, at the multivariate analysis (table 4), only the presence of general / non-specific complications was found to independently predict on maternal outcome (with an odds-ratio of 1.45 [95% CI 1.16-1.82] of a poor outcome); no other variables (treatment modality, timing and modality of delivery, trimester of presentation, clinical presentation and maternal) had a statistically significant influence on foetal outcome.

Unfortunately, there is little published data available as only single cases or very small series have been reported. Aside from overviews obtained from database registries [26], we found just 45 cases with detailed descriptions over the past 20 years during which coiling has been an established practice. The present cumulative series represents a synthesis of these cases and is the first with a statistical analysis and the first to describe aspects that are not available in other studies. However, because of the small case series, the statistical power of our findings in generally low (table 4), and thus our final findings and conclusions should be taken with caution.

Despite these limitations, we suggest a flowchart that summarizes the typical clinical management strategy for aSAH during pregnancy according to current published practice and our discussion (figure 1).

Conclusions

In conclusion, aSAH management and treatment strategy during pregnancy is still controversial. Early diagnosis and timely neurosurgical intervention can reduce the high maternal mortality and morbidity associated with aSAH. The choice of surgical treatment for securing the aneurysm and timing / mode of delivery should be evaluated on a case by case basis according to state of pregnancy, physiological condition and risk factors for the patient and for the foetus after a multidisciplinary assessment.

Further research in the field is warranted. Whilst a devastating disease, aSAH remains rare in pregnancy and this motivates the establishment of a multinational registry as one possible way in

which to obtain sufficient data to develop more robust guidance and better risk models that could inform clinical best practice.

Conflict of interest:
None to declare.

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Figures:

Figure 1. Flowchart describing the management strategies of aSAH patients during pregnancy. As for non pregnant patients, the priority is to secure of the aneurysm. During the first and second trimester, when the foetus is still premature, patients should be treated as non pregnants; thus, after the treatment of the aneurysm (clipping (clp) or endovascular (ev) according to the location and the characteristics of the aneurysm), the pregnancy should be continued without any further precautions, and the modality of delivery should be the physiological vaginal modality, at term. In the third trimester when the foetus is at term, a CS is raccomanded before or contemporary to treatment in order to avoid any further risks (radiations, anticoagulation etc..) for the baby.

Tab.1 Characteristics of the pregnant aSAH patients at presentation

Reference	Case n°	Mother age	PMH	Gesta-tional week	Tri-me-ster	Risk Factors	Symptoms at presentation	GCS at arrival	Hunt Hess Grade	Fisher Score
Kim et al., 2014 (24)	1	34	NA	16	2	NA	drowsiness, SZ	14	5	4
Surico et al., 2014 (52)	1	NA	hemangioblastoma, detected at SAH	27	3	NA	hypotension, SZ, neurological deterioration	NA	NA	3
Tarnaris et al., 2014 (53)	1	21	NA	29	3	NA	HA, third NP	15	3	NA
Kataoka et al., 2013(23)	1	20	NA	26	2	NA	left hemiparesis	12	NA	NA
	2	34	NA	30	3	NA	NA	14	NA	NA
	3	36	NA	24	2	NA	NA	15	NA	NA
	4	34	NA	31	3	NA	NA	15	NA	NA
	5	42	NA	28	3	NA	cardiopulmonary arrest	3	NA	NA
Bateman et al., 2012 (4)	1	41	NA	NA	3	age,african american race, eclampsia	SZ coma	3	5	4
	2	31	preeclampsia, HT	Post-partum	3	smoker, familiarity for ruptured aneurysm HT, preeclampsia	HA	15	2	NA
	3	42	negative	Post-partum	3	age	HA photophobia	15	2	<4
Guida et al., 2012 (16)	1	37	NA	34	3	NA	HA, V, nucal rigidity	15	2	4
	2	34	NA	37	3	NA	confusion, right hemiparesis	14	3	4
	3	41	NA	32	3	age	letargia, focal deficit (not specified)	12	3	3
	4	28	NA	33	3	NA	SZ	14	2	2
Ferreira et al., 2012 (13)	1	40	NA	32	3	NA	HA, gait imbalance	15	2	4
Elwatidy et al., 2011(12)	1	26	NA	36	3	NA	HA, meningism	15	2	NA
	2	24	NA	22	2	NA	HA, meningism LOC	15	2	<4
Pumar et al., 2010(43)	1	30	negative	22	2	NA	HA, V	15	NA	4
Darbhamulla & Reddy, 2007 (8)	1	22	HA	37	3	alchool abuse, HA	drowsiness, HA, neck stiffnes	15	NA	
Riviello et al., 2004 (44)	1	37	neg	36	3	no	HA, V, photophia	15	3	4
Roman et al., 2004 (45)	1	28	NA	35	3	NA	HA, confusion	14	3	4
	2	27	NA	34	3	NA	nucal rigidity, anisocoria	15	2	4
	3	37	NA	12	1	NA	dyplopia, retroorbital pain	15	2	NA
	4	30	HT	31	3	HT	SZ	14	3	NA
	5	30	NA	32	3	NA	HA, confusion, coma	3	5	4
	6	38	NA	38	3	NA	HA, coma	3	5	4

	7	33	HT	34	3	HT	cardiogenic shock, coma	3	4	4
Georgantopolou et al., 2003 (14)	1	32	NA	9	1	NA	HA, vomit, neck stiffness	15	2	<4
Kirzilikilic et al., 2003(27)	1	25	NA	10	1	NA	HA, neck stiffness, third NP	15	3	diffuse
	2	39	NA	18	2	NA	HA	15	2	4
	3	26	NA	28	3	NA	HA	15	2	NA
Hussain et al., 2001 (18)	1	29	NA	during labour	3	NA	HA, third NP	15	3	NA
Piotin et al., 2001(42)	1	28	NA	32	3	NA	HA, V	15	3	NA
	2	31	NA	22	2	NA	HA, V, LOC	15	3	NA
Shahabi et al., 2001 (48)	1	36	negative	38	3	no	HA, LOC	15	2	NA
Jaeger et al., 2000 (20)	1	38	NA	36	3	NA	HA, LOC	3	5	4
Meyers et al., 2000 (34)	1	34	NA	11	1	no	HA	15	2	3
	2	36	NA	NA	3	NA	HA	15	2	3
	3	36	NA	NA	3	NA	HA	15	2	diffuse
Barker et al.,1998 (2)	1	29	NA	35		NA	HA, V, photophobia, neck stiffness	15	2	4
D'Haese et al., 1997 (7)	1	29	NA	34	3	no	HA,V, anisocoria	15	3	NA
Kriplani et al., 1995(29)	1	25	negative	37	3	no	HA, neck stiffness	15	2	<4
	2	24	negative	36	3	no	HA, LOC	15	2	<4
	3	26	negative	36	3	no	HA, LOC, neck stiffness	15	3	4

PMH, past medical history; NA, not available; GCS, Glasgow Coma Score; SAH, Subarachnoid Haemorrhage; HA, headache; HT, hypertension;; NA, not available; NP, nerve palsy; HA, headache; LOC, loss of consciousness; PMH, past medical history; SZ, seizures; V, vomiting;

Tab.2 Management strategy and outcome in pregnant aSAH patients													
Reference	**Case n°**	**Tri-me-ster**	**Diagnostic modality**	**A. site**	**A. Treat-ment modality**	**CSF shunt**	**Timing of delivery**	**Modality of delivery**	**Emer-gency CS**	**General complications**	**Vaso-spasm**	**Out-come mother GOS**	**Outcome of the baby at birth APGAR**
Kim et al., 2014 (24)	1	2	DSA	PICA	EV		after tr.	cs	no	no		5	healthy
Surico et al., 2014 (52)	1	3	MRA & DSA	ICA	EV		after tr.	NA	no	no		4	9,9
Tarnariset al., 2014 (53)	1	3	MRA	PcomA	EV		after tr.	cs	no	no		5	healthy
Kataoka et al., 2013(23)	1	2	NA	VA-PICA	CLP		at term	cs	no	rerupture		5	healthy
	2	3	NA	AComA	CLP		contemp to tr.	cs	yes	cardiomyopathy	yes	5	healthy
	3	2	NA	MCA	CLP		contemp to tr.	cs	yes	septic shock	yes	5	healthy
	4	3	NA	AComA	CLP		contemp to tr.	cs	yes	no		5	healthy
	5	3	NA	BA	none		death in utero	none	no	cardiopulmonary arrest		1	death
Bateman et al., 2012 (4)	1	3	DSA	PComA	CLP		NA	NA	NA	NA		alive, death 7 days after discharge	NA
	2	3	DSA	Multiple	CLP		NA	NA	NA	NA		alive receptive aphasia	NA
	3	3	DSA	ICA	none		before tr.	cs	no	no		5	NA
Guida et al., 2012 (16)	1	3	DSA	ACA	CLP		before tr.	v	no	no	yes	5	NA
	2	3	DSA	MCA	EV		before tr.	cs	yes	died 2 days later		1	NA
	3	3	DSA	ACA	EV		before tr.	cs	yes	died 3 days later		1	NA
	4	3	DSA	BA	EV		before tr.	v	no	no		3	NA
Ferreira et al., 2012 (13)	1	3	DSA	VA-BA j	CLP	yes	NA	NA	NA	no	yes	5	NA
Elwatidy et al., 2011(12)	1	3	DSA	ICA	CLP		contemp to tr.	cs	yes	no		5	healthy
	2	2	DSA	MCA	EV		after tr.	v	no	no		5	healthy
Pumar et al., 2010	1	2	MRA	BA	EV		after tr.	cs	NA	NA		5	healthy

(43)													
Darbhamulla & Reddy, 2007 (8)	1	3	DSA	ACom A	EV	yes	after tr.	cs	yes	no		5	NA
Riviello et al., 2004 (44)	1	3	DSA	ACA	EV		before tr.	cs	yes	no		4	8,9
Roman et al., 2004 (45)	1	3	DSA	ICA	EV		before tr.	cs	yes	no	yes	5	5,10
	2	3	DSA	ICA	CLP	yes	after tr.	cs	yes	shunt		5	2,7 and 3,9 (twins)
	3	1	MRI (no CT)	ICA	CLP		after tr.	v	no	no		5	10,10
	4	3	CTA	ICA	CLP		before tr.	cs	yes	no		5	0,0
	5	3	DSA	MCA	none		before tr.	cs	yes	cerebral herniation pulmonary oedema		1	0,0
	6	3	CTA	MCA	none		death in utero	none	no	brain herniation		1	death in utero
	7	3	DSA	ICA	CLP		before tr.	cs	yes	brain herniation, rebleeding,		1	0,8
Georgantopolou et al., 2003 (14)	1	1	DSA	PCom A	CLP		after tr.	cs	no	osteomyelitis (bone flap)		5	healthy
Kirzilikilic et al., 2003(27)	1	1	MRA MRI DSA	PCom A	EV		aborted	none	no	no		5	aborted
	2	2	MRA MRI DSA	ICA	EV		after tr.	v	no	no		5	healthy
	3	3	MRI DSA	ACom A	EV		after tr.	v	no	no		5	healthy
Hussain et al., 2001 (18)	1	3	DSA MRI	PCA PCom A	no tr. (Throm-bosed)		no tr.	cs	yes	no		5	NA
Piotin et al., 2001(42)	1	3	MRA, DSA postpartum	ICA	EV		before tr.	cs	yes	no		5	healthy
	2	2	DSA	ICA	EV		at term	v	no	no		4	healthy
Shahabi et al., 2001 (48)	1	3	DSA	BA	EV		after tr.	cs	yes	no		5	good
Jaeger et al., 2000 (20)	1	3	DSA	ICA	CLP	yes	contemp to tr.	cs	yes	no		4	fair

Meyers et al., 2000 (34)	1	1	DSA	PCA	CLP followed by EV		after tr.	v	no	no		5	healthy
	2	3	DSA	BA	EV		after tr.	v	no	no		5	healthy
	3	3	DSA	PCom A	EV		before tr.	cs	yes	no		5	healthy (twins)
Barker et al., 1998 (2)	1	3	MRA MRI	PCom A	CLP		contemp to tr.	cs	yes	no		5	healthy
D'Haese et al., 1997 (7)	1	3	MRI MRA	ICA	CLP		contemp to tr.	cs	yes	no	yes	5	healthy
Kriplani et al., 1995(29)	1	3	DSA	ACom A	CLP		contemp to tr.	cs	yes	no		5	fair
	2	3	DSA	ICA	CLP		before tr.	v	no	no	yes	5	healthy
	3	3	DSA	PICA	CLP		contemp to tr	cs	no	rebleeding and hydrocephalus		5	healthy

Aneurysm; ACA, Anterior Cerebral Artery; AComA, Anterior Communicating Artery; A, BA, Basilar Artery; cs, C-section; CSF, cerebrospinal fluid; CLP, Surgical Clipping; CTA, contemp., contemporary; CTangiography; DSA, Digital Subtraction Angiography; EV, endovascular treatment; GOS, Gloasgow Outcome Score; ICA, Internal Carotid Artery; MR, Magnetic Resonance; MRA, Magnetic Resonance Angiography; NA, not available; PCA, posterior cerebral artery; PComA, Posterior Communicating Artery; PICA, PosterioInferior Cerebellar Artery; SIADH, Syndrome of Inappropriate Antiduretic Hormone Secretion; tr., treatment;v, vaginal delivery; VA Vertebral Artery

Parameter	**GOS 1-3** (n=8)	**n**	**GOS 4-5** (n=44)	**n**	**Statistical significance**[a]
Age (mean±SD; range; median)	35.88±5.38 (28-42; 36)	**8**	30.65±5.55 (20-42; median 30)	**44**	p-value=0.018
Gestational week (mean±SD; range; median)	33.43±3.36 (28-38; 33)	**7**	28.23±8.46 (9-39; median 31)	**39**	p-value=0.119
Trimester (n)	First (0); second (0); third (8)	**8**	First (4); second (10); third (30)	**44**	p-value=0.084
Aneurysmal site (n)	Anterior (6); posterior (2)	**8**	Anterior (34); posterior (10)	**44**	p-value=1.000
PMH (n)	Yes (1); no (not available)	**1**	Yes (6); no (12)	**18**	Not applicable
Risk factors (n)	Yes (3); no (not available)	**3**	Yes (10); no (8)	**18**	Not applicable
Treatment modality (n)	CLP (2); EV (3); none (3)	**8**	CLP (25); EV (16); none (3)	**44**	p-value=0.033
Modality of delivery (n)	Vaginal (1); caesarean (4); none (2)	**8**	Vaginal (11); caesarean (30); none (1)	**42**	p-value=0.027
Timing of delivery (n)	After treatment (0); at term (0); before treatment (5); contemporary to treatment (0) no treatment (2); aborted or death *in utero* (0)	**7**	After treatment (15); at term (7); before treatment (7); contemporary to treatment (11) no treatment (1); aborted or death *in utero* (1)	**42**	p-value=0.001
Vasospasm (n)	Not available		Yes (8); no (0)	**9**	Not applicable
General complications (n)	Yes (6); no (1)	**7**	Yes (10); no (33)	**43**	p-value=0.003
Emergency CS (n)	Yes (4); no (4)	**8**	Yes (19); no (22)	**41**	p-value=1.000
CSF shunt (n)	Not available		Yes (5); no (not available)	**5**	Not applicable
Hunt-Hess grade at arrival (mean±SD; range; median)	3.86±1.21 (2-5; 4)	**7**	2.49±0.69 (2-5; median 2)	**37**	p-value=0.004
Fisher score at	Equal to 4 (5); less than 4	**7**	Equal to 4 (18); less than 4 (10)	**28**	p-value=1.000

arrival (n)	(2)				
GCS at arrival (mean±SD; range; median)	6.88±5.38 (3-14; 3)	**8**	13.95±2.32 (3-15; median 15)	**43**	p-value <0.001
Parameter	**Apgar score 0-3** (n=7)	**n**	**Apgar score 4-10** (n=37)	**n**	**Statistical significance**[a]
Age (mean±SD; range; median)	32.86±6.18 (25-42; 30)	**7**	30.36±5.14 (20-39; median 30.5)	**36**	p-value=0.262
Gestational week (mean±SD; range; median)	26.57±11.10 (10-38; 31)	**7**	28.76±7.80 (9-39; median 30.5)	**36**	p-value=0.533
Trimester (n)	First (2); second (0); third (5)	**7**	First (2); second (9); third (25)	**36**	p-value=0.435
Aneurysmal site (n)	Anterior (6); posterior (1)	**7**	Anterior (29); posterior (8)	**37**	p-value=1.000
PMH (n)	Yes (1); no (not available)	**1**	Yes (3); no (9)	**12**	Not applicable
Risk factors (n)	Yes (1); no (not available)	**1**	Yes (7); no (8)	**15**	Not applicable
Treatment modality (n)	CLP (1); EV (3); none (3)	**7**	CLP (22); EV (15); none (0)	**37**	p-value <0.001
Modality of delivery (n)	Vaginal (1); caesarean (3); none (3)	**7**	Vaginal (9); caesarean (28); none (0)	**37**	p-value <0.001
Timing of delivery (n)	After treatment (1); at term (0); before treatment (3); contemporary to treatment (0) no treatment (3); aborted or death *in utero* (0)	**7**	After treatment (14); at term (7); before treatment (4); contemporary to treatment (12) no treatment (0); aborted or death *in utero* (0)	**37**	p-value <0.001
Vasospasm (n)	Yes (1); no (not available)	**1**	Yes (4); no (not available)	**4**	Not applicable
General complications (n)	Yes (3); no (4)	**7**	Yes (13); no (33)	**36**	p-value=0.419
Emergency CS (n)	Yes (3); no (4)	**7**	Yes (18); no (18)	**36**	p-value=1.000

CSF shunt (n)	Not available		Yes (4); no (not available)	**4**	Not applicable
Hunt-Hess grade at arrival (mean±SD; range; median)	3.50±1.22 (2-5; 3)	**6**	2.52±0.77 (2-5; median 2)	**31**	p-value=0.014
Fisher score at arrival (n)	Equal to 4 (4); less than 4 (not available)	**4**	Equal to 4 (17); less than 4 (9)	**26**	Not applicable
GCS at arrival (mean±SD; range; median)	9.57±6.16 (3-15; 14)	**7**	13.47±9.57 (3-15; median 15)	**36**	p-value=0.047

Table 3: statistical findings from pooled data analysis with respect to maternal and baby outcome. [a] Chi-squared test, exact Fisher's test, chi-squared test for trend for categorical data, t-test, U

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Parameter	F	Statistical significance[a]	Partial η^2	Observed power
Maternal outcome R^2=0.701 (adjusted R^2=0.552)				
Treatment modality	1.728	0.197	0.117	0.329
Timing of delivery	2.601	0.073	0.231	0.570
Modality of delivery	1.893	0.181	0.068	0.263
Hunt-Hess Grade	0.022	0.882	0.001	0.052
GCS at arrival	3.945	0.058	0.132	0.481
General complications	11.534	0.002	0.307	0.905
Trimester	0.044	0.957	0.003	0.056
Age	0.035	0.853	0.001	0.054
Baby outcome R^2=0.432 (adjusted R^2=0.268)				
Treatment modality	0.444	0.645	0.028	0.116
Timing of delivery	0.706	0.556	0.064	0.182
Modality of delivery	0.671	0.419	0.021	0.125
Hunt-Hess Grade	0.082	0.776	0.003	0.059
GCS at arrival	1.701	0.202	0.052	0.244

Table 4: statistical findings from the multivariate pooled data analysis with respect to maternal and baby outcome. [a]Generalized Linear Model. Also overall fitting raw and adjusted R^2, F-statistics, partial η^2 and observed power are reported.

Abbreviations: GCS (Glasgow Coma Scale).