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Early and Late Thunderclap Headache in Puerperium

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Abstract

Background and Aim of The Study: Prospective study on incidence of thunderclap headache in an unselected cohort of women during puerperium.

Material and Method: Nine-hundred consecutive women having given birth were prospectively enrolled in the study and examined within three days of delivery. A telephone interview was planned one month later.

Results: Thunderclap headache was recorded in 8 subjects (0.9%) on the first visit and in 33 (3.8%) at the one month follow-up interview. In all but one the course was spontaneously benign. None of the recorded variables allowed discriminating patients with thunderclap headache from those without headache. One patient was found to have reversible cerebral vasoconstriction syndrome (RCVS).

Headache with gradual onset was recorded in 80 (9.9%) patients at the basal visit and in 207 (23%) at the one month follow up. Three patients fulfilled the criteria for pre eclampsia. Predictors of early onset headache were age, ethnicity, haemoglobin levels and history of migraine. History of migraine, parity and proteinuria were predictors of late onset headache.

Conclusion: Puerperal headache has different clinical features and different predictors according to whether the onset is gradual rather than thunderclap and the occurrence is early vs. delayed. Primary headache accounted for the overwhelming majority of the recorded cases. Thunderclap headache presentation entails overall a benign prognosis. RCVS had an incidence of 0.1%.

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Introduction

Puerperium is a condition which poses women at a particularly high risk of suffering a number of different cerebrovascular insults [1-5]. In many of these, headache heralds the occurrence of more severe symptoms and signs and therefore represents a warning signal [6]. On the other hand, headache is one of the most commonly reported complaints in the first month post-partum [7-9]. In previously published series primary headache accounted for the vast majority of reports, but the retrospective nature of the collected cases or selection bias favouring inclusion of migraineurs limits the validity of the data [10,11]. The type of headache presentation may hint at the

possible underlying pathophysiological mechanism. Acute onset headaches, peaking in less than one minute, otherwise hinted at as thunderclap headache, are typically suggestive of subarachnoid haemorrhage, but may also be related to reversible cerebral vasoconstriction syndrome of which puerperium is an acknowledge precipitating factor [12-17]. Furthermore, a thunderclap presentation is reported in 2-10% of patients with cerebral venous sinus thrombosis, 20% of patients with cervical artery dissection and less frequently in ischaemic stroke, retroclival haematoma, pituitary apoplexy and third-ventricle colloid cyst [18]. Primary thunderclap headache with no associated brain abnormality is being recognized as a clinical entity as well, although as a last resort diagnosis only after all possible alternative causes have been ruled out with an appropriate diagnostic work up [12,18].

We undertook the present study with the primary aim of prospectively assessing the incidence of brain vasospatic syndrome during puerperium (VASP) in a consecutive series of women having given birth to a baby, the results of which are reported elsewhere [19]. In the present paper we report the results of headache prevalence in the first month post-delivery with particular emphasis on the thunderclap presentation as a warning signal for VASP.

Material and Methods

The study period extends from November 2011 to July 2013. We studied all female subjects having given birth to a baby in the Obstetrics Department of the S. Orsola Hospital (first 86 cases, then Poliambulanza Hospital, as the former was incorporated in the latter) in Brescia, Italy. The subjects underwent a basal visit within 96 hr of delivery, in which a chart review was performed and a structured interview was administered in person by one research assistant, with particular emphasis on headache. Thereafter, ABP was measured noninvasively and a transcranial ultrasound study was performed.

The study protocol was approved by the S. Orsola Hospital Institutional Review Board. All patients provided informed consent before entering the study. Information was collected on maternal demographics, labour and delivery details, anaesthesia during labour and delivery and headache characteristics and management. The following data were also collected: age, ethnicity, height, weight gain, arterial blood-pressure, history of primary headache disorders, history of arterial hypertension, smoking habits, alcohol intake, diabetes, dyslipidemia, family history of stroke and detailed characteristics of recent pregnancy and delivery, including medications and drugs taken during pregnancy. We also recorded in all subjects haemoglobin, uric acid and proteinuria levels. Headache intensity was evaluated by using a visual analog scale ranging from 0 (no pain) to 10 (the worst pain that you can ever imagine). Regarding the onset, headache attacks reaching a maximum intensity above 7/10 in less than 1 min were qualified as 'thunderclap headache' whereas those peaking more slowly as 'gradual onset headache". Headache pain was systematically classified whenever possible as pulsating, pressing-tightening or neuralgic. When headache turned out to be unrelated to intracranial pathology it was diagnosed according to the 2013 criteria of the International Headache Society [12].

A basal assessment with Transcranial Colour-Coded Sonography (TCCS) was performed in all patients to detect any early sign of vasospasm by using a Philips IU 21 device. The M1 and M2 segments of the middle cerebral artery (MCA) were identified, and mean flow velocity (MFV) was recorded [20]. MFV of 100 cm/sec was selected as the normal upper limit in this study [21]. In patients with MCA velocity exceeding the threshold, we also calculated Lindegaard Index (LI) by dividing the MFV in MCA by the mean flow velocity of ipsilateral distal extracranial ICA. Published studies have indicated that an LI of 3 to 6 can be considered as mild vasospasm and greater than 6 can be considered moderate-to severe vasospasm [22].

All subjects were further instructed to pay special attention to the occurrence of sudden thunderclap headache in the following month and in case to access the Emergency Ward of the Hospital for expedited assessment or to contact by phone one of the study researchers.

To ensure complete ascertainment all the participants were reassessed at one month after hospital discharge by a structured telephone interview inquiring about the occurrence and detailed characteristics of any type of headache, focal neurological deficits and seizures since delivery. Patients answering positively were invited to a neurological examination including transcranial Doppler within few days and again, those fulfilling the criteria for brain vasospasm underwent MRI scan including MRA.

Continuous variables were compared by mean of two-tailed T test if normally distributed or with Mann-Whitney test if the distribution was not normal. Frequencies were compared by Pearson Chi square test. Multiple logistic regression was used to assess predictors of headache encountered on the basal assessment or recorded on follow-up (SPSS version 22).

Results

During the inclusion period of 20 months, 900 women were enrolled in the study: 75% of them were of Caucasian ethnicity, mean age was 31 + 5 (range 16-45), 53% at their first pregnancy, 32% at the second one, the remaining 15% being distributed to up to six previous pregnancies. They were evaluated at a mean of 1.5 + 1 days post-partum (range 0-11), and follow-up telephone interview occurred on the average 39 + 11 days (range 25-50) after childbirth. Past history for headache was available in 850 subjects: 292 (34.4%) were migraine sufferers and 164 (19.3%) reported tension-type headache in past history. On the first visit, overall 88 (9.8%) women reported headache, 8 (0.9%) with thunderclap and 80 (9.9%) with gradual onset. Median intensity was 5 in thunderclap and 4 in gradual onset.

When headache had started as a thunderclap it was pulsating in 4 (50%) and pressing-tightening in the remaining 4 (50%) patients, whereas when onset had been gradual it was pulsating in 20 (25%) subjects, pressing-tightening in 56 (70%), neuralgic in 2 (2.5%) and undetermined in 2 (2.5%), but the difference in type distribution was not statistically significant (p= 0.646). Overall, pressing-tightening headache accounted for 60/88 (68%) of all cases.

Postural worsening of headache in upright position was noticed in overall 16/88 (18%) women, in 3/8 (37.5%) subjects with thunderclap presentation and in 13/80 (16.2%) with gradual onset (p = 0.320). Comparing women with headache with those without for past history, migraine was more frequent in patients with than in those without headache (53.7% vs. 31.9 % p < 0.0001). Ethnicity was also significant, as women from east Europe or South America were more likely to develop headache compared with other ethnicities (27.25% on the average vs. 9.9%, p = 0.012). Comparing for biological variables, only diastolic blood pressure measured on the day of delivery was significantly higher in patients with than in those without headache (74 + 10 Hg/mm vs. 71 + 9 Hg/mm respectively p = 0.003) and the same trend, although not significant, was apparent also for systolic blood pressure (115 + 17 vs. 112 + 14 Hg/mm respectively, p=0.1). Intracranial MFV tended to be higher in patients with headache compared with headache free subjects (right M1 77 + 19 vs.73 + 17, right M2 74 + 19 vs. 73 + 17, left M2 76 + 23 vs. 72 + 17) but only for left M1 (78 + 20 vs.73 + 17) the difference was statistically significant (p=.047). Finally, Haemoglobin showed a trend for being lower in headache subjects (11.1 + 1.6 vs 11.4 + 1.3, p= 0.065) and age to be higher (32 + 6 vs. 31 + 5 p = 0.083).

A regression analysis was performed with headache as dependent variable and factors that had been significant on univariate analysis or known from the literature to predict post-partum headache as independent variable (table1). Age, history of migraine, ethnicity and Haemoglobin level turned out as independent predictors of early headache.

None of the 8 subjects who reported having suffered from a thunderclap headache soon after delivery had neurological abnormalities nor ultrasound findings suggestive of vasospasm. During the follow-up period six women contacted the research staff for the occurrence of headache with hyper acute onset. They were all examined and subjected to MRA: both clinical, neurosonological and neuroradiological findings were within normal limits in 5, whereas one case fulfilled the criteria for reversible cerebral vasoconstriction syndrome (RCVS). This case is reported in a separate paper [19].

On final follow-up interview, 241 subjects (26.8%) reported having had at least one headache attack since delivery, in 34 of them (3.8%), including the case with RCVS, with features of thunderclap headache. Apart from the RCVS case and the five women examined during follow up, none of the remaining 28 women with thunderclap headache ever accessed Emergency Ward or sought medical advice, all were free of headache at the time of follow-up and none reported focal deficits.

Median intensity of attacks presenting as thunderclap was 7, whereas in attacks with gradual onset it was 5 ($p < 0.0001$). Pain was pulsating or neuralgic in 25/34 (73.5%) cases of thunderclap presentation and pressing-tightening in the remaining 9 (26.5%), whereas when onset was gradual, pain was reported as pulsating or neuralgic in 87/207 (42%) and pressing-tightening in the remaining 120 (58%), this difference being statistically significant ($p < 0.0001$). Among patients with gradual onset headache, 3 (1 with pulsating and 2 with pressing-tightening headache) fulfilled the criteria for pre-eclampsia (i.e proteinuria and hypertension at the end of pregnancy) and were therefore considered apart and excluded from subsequent analyses.

Univariate analyses were conducted separately for subjects with gradual onset and thunderclap headache in comparison with women who had not had headache during follow up. None of the variables assessed at baseline, including history of migraine, differentiated patients with thunderclap headache from those without headache on follow–up, whereas history of migraine was significantly more frequent and proteinuria higher in subjects with gradual onset headache (table 2). Parity showed a non-significant trend for a protective effect: the higher the parity the lower the likelihood for gradual onset headache to occur (26.2 % on the average until 3rd pregnancy vs. 16.4% form the 4th pregnancy onward, data not shown in the table).

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for O.R.	
		B	Std. Error	O.R.			Lower Bound	Upper Bound
1	(Constant)	-0.262	0.173		-1.514	0.130	-0.602	0.078
	History of migraine	0.087	0.026	0.135	3.342	0.001	0.036	0.139
	Type of delivery	0.007	0.018	0.017	0.397	0.691	-0.028	0.042
	Age	0.007	0.003	0.110	2.509	0.012	0.001	0.012
	BMI	0.003	0.003	0.043	1.038	0.300	-0.003	0.010
	Ethnicity	0.019	0.007	0.116	2.808	0.005	0.006	0.032
	Parity	0.000	0.015	-0.003	-0.064	0.949	-0.030	0.028
	Ergot during delivery	0.003	0.008	0.016	0.387	0.699	-0.012	0.018
	Hb.	-0.019	0.009	-0.082	-2.021	0.044	-0.037	0.000
	Proteinuria (mg/dl)	0.000	0.001	0.024	0.565	0.572	0.000	0.002
	Syst. BP on delivery	0.000	0.001	-0.015	-0.263	0.792	-0.003	0.002
	Diast. BP on delivery	0.004	0.002	0.110	1.907	0.057	0.000	0.007

BMI = body mass index

Hb. = Haemoglobin concentration

Syst. BP = systolic blood pressure

Diast. BP = diastolic blood pressure

Table 1: *Multiple regression analysis. Headache on basal assessment as dependent variable.*

	A	B	C	
	No headache n. = 659	**Thunderclap headache n. = 34**	**Gradual onset headache n. = 207**	**P**
BMI	23 + 4	23 + 4	23 + 4	NS
AGE	31 + 5	30 + 6	31 + 2	NS
Weight gain in Kg	13 + 5	12 + 4	13 + 4	NS
Right M1 MFV	74 + 17	75 + 15	74 + 20	NS

Right M2 MFV	72 + 17	75 + 20	74 + 18	NS
Left M1 MFV	73 + 17	78 + 17	75 + 20	NS
Left M2 MFV	72 + 17	76 + 18	75 + 18	NS
Syst. BP	111 + 12	112 + 12	112 + 14	NS
DIASt. BP	68 + 9	70 + 8	71 + 9	NS
Hb.	11.3 + 1.3	11.3 + 1	11.4 + 1.5	NS
Proteinuria mg/dl	6.8 + 13	6.0 + 9	11.7 + 34	A vs. C = 0.001
History of migraine	29.9%	30.3%	48.5 %	A vs. C <0.0001
Present or past-preeclampsia	4%	2.9%	3.9%	NS
Spinal anaesthesia	15.5%	14.7%	11.7%	NS

BMI = body mass index

Hb. = Haemoglobin concentration

Syst. BP = systolic blood pressure

Diast. BP = diastolic blood pressure

MFV = mean flow velocity

M1 = proximal segment of the middle cerebral artery

M2 = distal segment of the middle cerebral artery

Table 2: *comparison between subjects who reported on follow up the occurrence of thunderclap headache or gradual onset headache and women without headache for potentially meaningful variables assessed at baseline.*

On multiple regression analysis there was no independent predictor of thunderclap headache, whereas past migraine, proteinuria and parity were independent predictors of gradual onset headache (Tables 3 and 4). In patients with gradual onset headache a further analysis was performed: those who reported pulsating pain had a significantly more frequent history of migraine (61.4% vs. 39.4%, p = 0.003) and were less likely to be at their first pregnancy (33% vs. 66.7% p = 0.04) compared with those with pressing-tightening pain (data not shown).

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for O.R.	
		B	Std. Error	O.R.			Lower Bound	Upper Bound
1	(Constant)	-0.017	0.129		-0.134	0.894	-0.270	0.236
	History of migraine	-0.008	0.020	-0.019	-0.401	0.689	-0.047	0.031
	Syst. BP on basal visit	6.676E-5	0.001	0.004	0.065	0.948	-0.002	0.002
	Diast. BP on basal visit	0.000	0.001	-0.010	-0.154	0.877	-0.003	0.003
	Type of delivery	-0.011	0.013	-0.045	-0.895	0.371	-0.036	0.014
	Age	0.001	0.002	0.035	0.662	0.508	-0.002	0.005
	BMI	0.002	0.002	0.041	0.814	0.416	-0.003	0.007
	Ethnicity	0.002	0.005	0.016	0.324	0.746	-0.008	0.011
	Parity	0.000	0.010	-0.004	-0.072	0.943	-0.021	0.019
	Ergot during delivery	0.003	0.006	0.030	0.599	0.550	-0.008	0.015
	Hb	-0.001	0.007	-0.008	-0.160	0.873	-0.015	0.012
	Proteinuria (mg/dl)	0.000	0.001	0.011	0.220	0.826	-0.001	0.001

BMI = body mass index

Hb. = Haemoglobin concentration

Syst. BP = systolic blood pressure

Diast. BP = diastolic blood pressure

Table 3: *Multiple regression analysis. Thunderclap headache on follow-up as dependent variable.*

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for O.R.	
		B	Std. Error	O.R.			Lower Bound	Upper Bound
1	(Constant)	1.698	0.252		6.731	0.000	1.202	2.193
	History of migraine	-0.158	0.037	-0.179	-4.228	0.000	-0.231	-0.085
	Syst. BP on basal visit	3.735E-5	0.002	0.001	0.019	0.985	-0.004	0.004
	Diast. BP on basal visit	0.002	0.003	0.051	0.857	0.392	-0.003	0.008
	Type of delivery	0.032	0.025	0.055	1.252	0.211	-0.018	0.081
	Age	-0.006	0.004	-0.069	-1.521	0.129	-0.013	0.002
	BMI	0.000	0.005	0.002	0.035	0.972	-0.009	0.009
	Ethnicity	-0.002	0.009	-0.009	-0.204	0.838	-0.020	0.017
	Parity	0.046	0.020	0.101	2.278	0.023	0.006	0.086
	Ergot during delivery	0.000	0.011	0.000	0.010	0.992	-0.022	0.022
	Hb.	0.004	0.013	0.014	0.324	0.746	-0.021	0.029
	Proteinuria (mg/dl)	-0.002	0.001	-0.111	-2.583	0.010	-0.004	0.000

Hb. = Haemoglobin concentration

Syst. BP = systolic blood pressure

Diast. BP = diastolic blood pressure

Table 4: *Multiple regression analysis. Gradual onset headache on follow-up as dependent variable BMI = body mass index.*

Discussion

The present study was primarily undertaken to assess the incidence of puerperal vasospastic syndrome (VASP), of which the heralding most important sign is headache with thunderclap features. By emphasizing the occurrence of headache as warning signal for VASP we were thus able to study the timing and characteristics of any headache occurring in the first month post-delivery. Following the study protocol, type of presentation (gradual vs. thunderclap), type of pain (pulsating vs. pressing-tightening) and pain intensity were systematically assessed in the entire cohort of women at two study points, within three days of delivery and one month later.

Early onset headache was noticed in about 10% of women, most often with moderate severity, gradual onset and non-pulsating features, thus reminiscent of the characteristics of tension-type headache [12]. Women from East Europe and South America appeared to be particularly prone to develop early postpartum headache, as well as migraine sufferers independently of ethnicity. It is unclear whether this particular propensity of some ethnicities , which, to the best of the authors' knowledge has never been reported, has to do with a genetical predisposition to tension-type headache or rather with socio-economical factors contributing to an increased level of post-partum stress. A constitutional susceptibility towards early post-partum headache is highlighted by the independent effect of past migraine, which has been consistently confirmed in all studies [7,8,9,23,24], even though headache characteristics in the very early puerperal period were closer to tension-type than to migraine. This too had been noticed previously [24].

Of the physiological variables significantly associated with headache on univariate analysis (haemoglobin, blood pressure and blood flow velocity in brain vessels) only haemoglobin remained significant on regression analysis: this most likely because both the increase in diastolic blood pressure and the increase in blood flow velocity occurred as a physiological consequence of the blood loss during delivery [25]. Therefore iron deficiency acute anemia seems the most logical mechanism underlying increased intracranial velocities and mild hypertension and ultimately enhancing the appearance of headache [26].

Increasing age has been recognized as a risk factor for early post-partum headache and the effect attributed to higher anxiety in older mothers because of fewer chances to get help from parents once returned at home [7-10]. The age effect was confirmed in our findings, although for unclear reasons. It is of notice that women with early headache were only one year older, on the average, than women without headache, thus making any interpretation debatable.

Factors traditionally supposed to enhance or directly cause post-partum headache, such as spinal anaesthesia, use of ergot derivatives after delivery and past or present history of pre-eclampsia were irrelevant so as to the occurrence of early headache. Post dural puncture headache has been linked to operator inexperience in teaching hospitals hence leading to a CSF loss and postural headache [7]. Although 18% of women reported a postural worsening of headache in upright position on basal assessment, in none of them the further course was suspicious for intracranial hypotension syndrome and spinal anaesthesias were delivered by experienced anaesthesiologists. Therefore we don't believe that CSF loss played any role in triggering headache in subjects reporting postural worsening.

Out of 900 women of the present cohort only 10 fulfilled criteria for pre-eclampsia; of these only 3 complained of early headache and past history for pre-eclampsia was no more frequent in subjects with (4.1%) than without (3.9%) headache (data not shown). The rarity of preeclampsia cases explains why in our series this was not a significant predictor of headache.

Ergot derivatives were administered in overall 500 women, but headache occurred with the same frequency in those who were and in those who were not treated (about 10%). In summary, early post-delivery headache was noticeable in 10% of women, it was most often of gradual onset and with tension-type features, although some cases had a thunderclap presentation. In no case, however, was the clinical picture suspicious for brain pathology, history of migraine and anaemia were the most important risk factors, whereas ethnicity and age played a questionable role.

By the end of follow up, the number of subjects who had had headache rose to 241 (26.8% of the entire cohort). Of these 34 (3.8% of the total) had a thunderclap presentation and one developed the VASP syndrome. In the remaining 33 the course, as assessed by the end of follow-up interview, was benign with spontaneous remission and no clinically suspicious sign or symptom. In five of them a clinical, neurosonological and neuroradiological assessment did not reveal any structural abnormalities. Overall pain was severe (7 on the 0-10 scale) and pulsating in the majority of cases. Neither univariate nor regression analysis identified any meaningful risk factor (see table 2 and 3).

On the contrary, of the 207 patients with gradual onset headache, median severity was moderate (5 on the 0-10 scale) and pain characteristics quite evenly distributed between pulsating and pressing- tightening. History of migraine was a significant overall predictor in comparison with subjects who did not develop headache, and it turned out to be significantly more frequent in patients with pulsating (66.7%) than in those with pressing tightening (33%) headache. In a further regression analysis (shown in the supplementary table), past migraine was the only factor discriminating pulsating from pressing tightening headache in subject who complained of gradual onset headache.

Proteinuria at the end of pregnancy was significantly higher in patients with gradual onset headache compared with subjects headache free, was an independent predictor of gradual onset headache on regression analysis but did not discriminate pulsating from pressing-tightening headache when onset was gradual (see supplementary table and tables 2 and 4). Proteinuria is a cardinal sign of pre-eclampsia [27], but, as discussed above, only 10 patients fulfilled the criteria for pre-eclampsia and of them only 3 complained

of headache. We therefore speculate that proteinuria, which was recorded in 241 patients in significant amounts (> 10 mg/dl) might represent a marker of minor endothelial dysfunction related to terminal pregnancy even in the absence of overt signs of pre-eclampia [28]. Migraine too has been linked to endothelial dysfunction, although the evidence is controversial [29,30] and is recognized as a risk factor for pre-eclampsia [31]: it is thus possible that minor endothelial dysfunction in the presence of history of migraine may have lowered the threshold for developing headache in our patients with significant proteinuria. Indeed, compared with subjects without proteinuria and without history of migraine, those who had both conditions developed post-partum headache in 40% vs. 18.1% of cases ($p < 0.0001$ – data not shown)

On univariate analysis parity showed a non-significant protective effect, as women with parity > 3 tended to complain less frequently of headache. Regression analysis confirmed parity among independent predictors of gradual onset headache. An opposite effect of parity compared to that found in the present study, in that parity was associated with an increased risk of headache, was noticed by others [7,24]. The different timing of data collection, which was within 7 days post childbirth in both paper, may partly explain the discrepancy.

Overall, our findings were consistent with the literature in demonstrating that headache is a very early complaint in about 10% among women who have just given birth, but contrary to others [7,8]. we found that incidence rises to up about 27% in the 4 weeks post childbirth. Overall this figure is in the range of previous reports that had found an incidence of 11%-39% [7]. Compared with the only study that examined patients in the early post-partum period we found a lower incidence (9.8% vs. 38.7%), but in Goldszmidt 's study the assessment was performed on the average 7 days post-partum whereas in the present study it occurred 1.5 days after childbirth [7].

Post-partum headache has a number of possible etiologies [6,32]., but most often it occurs without demonstrable brain pathology, hence the definition of primary headache. In a prospective series of 985 women interviewed with 7 day s of delivery, Goldszmidt., *et al*. [7] found that tension-type headache alone accounted for 38.3% of all reported headaches, followed by migraine (overall 34.1%) and other ill-defined primary headaches, the only secondary cases being referred to post dural puncture (overall 4.7% of cases). On the other hand, Stella., *et al.* [8], although confirming tension-type as the most frequent postpartum headache (39%), found that in 45% of cases headache was secondary to a brain disease (pre-eclampsia 24%, post dural punction 16%, pituitary pathology 3%, cerebral venous thrombosis 3%, cerebral vasculopathy 2%, thalamic lesion 1%, subarachnoid haemorrhage 1%) in 95 hospitalized patients. Clearly, a selection bias favouring the most severe or suspicious cases of headache explain the different distribution between primary and secondary headache types.

In the present study we were primarily focused on the detection of VASP, the main heralding symptoms of which is thunderclap headache. Therefore we put a special emphasis on headache presentation as a basic clue to diagnosis, by separating headaches with sudden from those with gradual onset. Furthermore we assessed headache prevalence at two distinct study points, early post-delivery and one month later. This allowed a more precise characterization of headache types and relative risk factors. Overall, the overwhelming majority of recorded cases were attributable to primary headache, as we found only one case of reversible cerebral vasoconstriction syndrome (1/900 = 0.1%) and only 3 cases (3/900 = 0.3%) in whom headache occurred in patients with pre-eclampsia. Although postural worsening was reported in 18% of 88 patients with headache on the first assessment, in no case the clinical picture and course suggested intracranial hypotension as the pathophysiological mechanism and postural headache had the same prevalence in patients who had undergone spinal anaesthesia as in those who had not, which is why we did not consider post dural punction as a reasonable cause in any of the reported cases.

Headache occurring in the very early period post-delivery and that occurring later in the course of follow up shared the same distribution of type of presentation, being in both instances 90% gradual and 10% with thunderclap onset. However, early and late headache presentations showed differences in headache features (more often pressing-tightening in early presentation) and in associated abnormalities and predictors: while history of migraine was significant for both early and late presentation, ethnicity and haemoglobin levels were only significant for early presentation, whereas proteinuria and parity predicted late presentation with gradual onset. This

suggests that the mechanisms underlying the appearance of headache may be different in early as compared to late presentation. In early occurring headache the clinical presentation and associated abnormalities suggest that the aetiology was primarily dependent on early physiological changes that take place after delivery and the headache was mainly tension-type, whereas in late presentation two distinct types of headaches accounted for the majority of cases: a tension-type headache, presenting with gradual onset and pressing-tightening features (118/900 = 13.1% of the entire cohort) and a migraine-like pulsating headache (86/900= 9.6 % of the entire cohort). Overall they shared migraine history, proteinuria and parity as independent predictors, but migraine history differentiated pulsating from pressing-tightening clinical features. Therefore we believe that in late onset headache migraine resurgence explains a significant proportion of cases whereas tension-type headache arises as a possible consequence of the psychological pressure imposed by motherhood.

This interpretation is supported by the findings of the parity effect in our sample. The higher the parity, the less was the likelihood of getting headache as a whole, but when headache occurred it was more often pulsating, which means that more experienced women (those with more past pregnancies) were less likely to develop headache as a response to the anxiety/stress generated by parturition and more likely to experience the resurgence of migraine compared with women at their first experience in whom tension-type headache predominated.

Thunderclap headache accounted for 9% (8/88) of early and 14% (34/238) of late onset headache cases, it had a benign course in the overwhelming majority (33/34–97%) of occurrences and did not share any risk factor with gradual onset headache. Indeed, we were unable to find out any meaningful association with variables known to affect headache incidence. For this reason we classified thunderclap headache as a separate clinical entity (see table 5).

		n.	%	RF
Primary headache	Tension-type	118	13.1	Past migraine. Proteinuria, Parity
	Migraine-like	86	9.6	Past migraine, Proteinuria, Parity
	Thunderclap	33	3.7	None identified
Secondary headache	Pre-eclampsia	3	0.3	Proteinuria, hypertension
	VASP	1	0.1	None identified
No headache		659	73.2	NA
	TOTAL	900	100	

RF: Risk Factors

NA: Non Applicable

Table 5: *Headache incidence and Risk factors as assessed at the 30 day follow-up.*

One patient with thunderclap headache was found to be affected by reversible cerebral vasoconstriction syndrome, which, however had a very favourable course with no residual deficit. The remaining 33 cases were assessed clinically and instrumentally in 5 instances and showed normal findings, in the remaining cases the diagnosis of thunderclap headache was put forward at the follow-up interview as all the subjects had had a favourable course had not sought medical advice and were symptom free at the time of the interview. It may be questioned whether these 33 cases represent true primary headache examples or rather minor manifestation of benign vasospastic syndrome. Whatever the cause, however, the clinical course was benign and the headache subsided without any residual deficit, which by itself rules out other potentially catastrophic aetiologies [18].

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for O.R.	
		B	Std. Error	O.R.			Lower Bound	Upper Bound
1	(Constant)	2.298	0.673		3.416	0.001	0.964	3.632
	History of migraine	-0.359	0.092	-0.366	-3.904	0.000	-0.542	-0.177
	Syst. BP on basal visit	0.008	0.005	0.204	1.581	0.117	-0.002	0.018
	Diast. BP on basal visit	-0.010	0.007	-0.179	-1.408	0.162	-0.024	0.004
	Type of delivery	-0.062	0.074	-0.081	-0.830	0.408	-0.209	0.086
	Age	0.003	0.010	0.032	0.318	0.751	-0.017	0.023
	BMI	-0.017	0.013	-0.128	-1.341	0.183	-0.043	0.008
	Ethnicity	-0.001	0.023	-0.004	-0.050	0.961	-0.048	0.045
	Parity	-0.089	0.062	-0.142	-1.438	0.154	-0.212	0.034
	Ergot during delivery	0.012	0.028	0.040	0.434	0.665	-0.043	0.067
	Hb.	-0.021	0.029	-0.068	-0.733	0.465	-0.079	0.036
	Proteinuria (mg/dl)	-9.800E-5	0.001	-0.006	-0.068	0.946	-0.003	0.003

BMI = body mass index

Hb. = Haemoglobin concentration

Syst. BP = systolic blood pressure

Diast. BP = diastolic blood pressure

Supplementary Table: *multiple regression analysis comparing, in patients with gradual onset headache, pulsating vs. pressing-tightening pain.*

In summary, our findings suggest that headache during puerperium has different clinical features different predictors according to whether the onset is gradual rather than thunderclap and the occurrence is early vs. delayed. Primary headache (migraine-like or tension-type) accounted for the overwhelming majority of the recorded cases in our cohort. Thunderclap headache presentation, far from being a rarity, appears to entail overall a benign prognosis, but timely appropriate investigations are to be performed to identify those cases in whom the underlying mechanism resides in vasoconstriction of cerebral vessels [34].

Merits of the present study are the prospective nature, the large cohort size and the systematic investigation of all included cases and follow up with no lost, which allowed complete case ascertainment. The main limit of the study was that it was based on a single centre experience.

References

1. Del Zotto E., *et al*. "Ischemic Stroke during Pregnancy and Puerperium". *Stroke Research and Treatment* 2011 jan 27; 2011:6060780.
2. Cantu-Brito C., *et al*. "Cerebrovascular complications during pregnancy and postpartum: clinical and prognosis observations in 240 Hispanic women". *European Journal of Neurology* 18.6 (2011): 819-825.
3. Khan M and Wasay M. "Haemorrhagic strokes in pregnancy and puerperium". *International Journal of Stroke* 8.4 (2013): 265-272.
4. Schebesch KM., *et al*. "Subarachnoid Hemorrhage from Posterior Cerebral Artery Aneurysm during Puerperium – Case Report and Review of Literature". *Journal of Neurology & Neurophysiology* 3 (2012): 1-3.
5. Seo P. "Pregnancy and Vasculitis". *Rheum Dis Clin N Am* 33 (2007) 299–317.
6. Lim SY., *et al*. "Postpartum headache: Diagnostic Considerations". *Practical Neurology* 14.2 (2014): 92-99.
7. Goldszmidt E., *et al*. "The incidence and etiology of postpartum headaches: a prospective cohort study". *Canadian Journal of Anesthesia* 52.9 (2005): 971-977.

8. Stella CL., *et al*. "Postpartum headache: is your work-up complete?" *American Journal of Obstetrics & Gynecology* 196.4 (2007): 318. e1-318.e7.
9. Scharff L., *et al*. "Headache during pregnancy in the postpartum: a prospective study". *Headache* 37.4 (1997): 203-210
10. Hoshiyama E., *et al*. "Postpartum Migraines: A Long-term Prospective study". *Internal Medicine* 51.22 (2012): 3119-3123.
11. Kvisvik EV., *et al*. "Headache and migraine during pregnancy and puerperium: the MIGRA-study". *The Journal of Headache and Pain* 12.4 (2011): 443–451.
12. Headache classification subcommittee of the International Headache Society. The international classification of headache disorders, 3rd edition. Cephalalgia 2013; 33: 629–808.
13. Ducros A., *et al*. "The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome: a prospective series of 67 patients". *Brain* 130.pt 12 (2007): 3091-3101.
14. Calabrese LH., *et al*. "Narrative Review: Reversible Cerebral Vasocontriction Syndromes". *Annals of Internal Medicine* 146.1 (2007): 34-44.
15. Singhal AB., *et al*. "Reversible cerebral vasoconstriction syndromes: analysis of 139 cases". *Archives of Neurology* 68.8 (2011): 1005-1012.
16. Ducros A. "Reversible cerebral vasoconstriction syndrome". *Lancet Neurology* 11.10 (2012): 906-917.
17. Skeik N., *et al*. "Postpartum reversible cerebral vasoconstriction syndrome: Review and analysis of the current data". *Vascular Medicine* 20.3 (2015): 256-265.
18. Schwedt TJ., *et al*. "Thundereclap headache". *Lancet neurology* 5.7 (2006): 621-631.
19. Anzola GP., *et al*. "Reversible cerebral vasoconsctriction syndrome in puerperium: a prospective study". *Journal of the Neurological Sciences* 375 (2017): 130-136.
20. Bartels E. "Color-Coded Duplex Ultrasonosgraphy of the cerebral vessels7Atlas and manual". *Schattauer. Stuttgart* 1999.
21. Felberg RA., *et al*. "Screening for Intracranial Stenosis with Transcranial Doppler: The Accuracy of Mean Flow Velocity Thresholds". *Journal of Neuroimaging* 12.1 (2002): 1-6.
22. Lindegaard KF., *et al*. "cerebral vasospasm diagnosis by means of angiography and blood velocity measurements". *Acta Neurochirurgica* 100.1-2 (1989): 12-24.
23. Stein GS. "Headaches in the first post-partum week and their relationship to migraine". *Headache* 21 (1981): 201-205
24. Stein G., *et al*. "Headaches after childbirth". *Acta Neurologica Scandinavica* 69 (1984): 74-79.
25. Brass L M., *et al*. "Transcranial Doppler measurements of the middle cerebral artery". *Effect of hematocrit Stroke* 19.2 (1988): 1466-1469.
26. Krayenbuehl PA., *et al*. "Iron deficiency anemia in adults. Main symptoms: fatige, pallor, (stress-) dyspnea, headache, concentration disorders". *Praxis* (bern 1994) 96.34 (2007): 1241-1247.
27. Sibai BM. "Diagnosis, prevention, and management of eclampsia". *Obstetrics & Gynecology* 105.2 (2005): 402–410
28. Cindrova- Davies T. "Gabor Than Award Lecture 2008: Pre-Eclampsia – From Placental Oxidative Stress to Maternal Endothelial Dysfunction". *Placenta* 30.Supplement A (2009): S55–S65.
29. Schwedt TJ. "Endothelial dysfunction in migraine". *Cephalalgia* 29.9 (2009): 997-1002.
30. Butt JH., *et al*. "Endothelial function in migraine with aura - a systematic review". *Headache* 55.1 (2015): 35-54.
31. MIGEPE Simbar M., *et al*. "Increased risk of pre-eclampsia (PE) among women with the history of migraine". *Clinical and Experimental Hypertension* 32.3 (2010): 159-165.
32. Sabharwal A and Stocks GM. "Postpartum headache: diagnosis and pain management". *Continuing Education in Anaesthesia, Critical Care & Pain* 5 (2011): 181-185.
33. Chen SP., et al. "Transcranial color Doppler study for reversible cerebral vasoconstriction syndromes". *Annals of Neurology* 63.6 (2008): 751–757.
34. Miller TR., *et al*. "Reversible Cerebral Vasoconstriction Syndrome, Part 2: Diagnostic Work-Up, Imaging Evaluation, and Differential Diagnosis". *AJNR* 36.9 (2015): 1580-1588.