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ABSTRACT

Objectives

The aim of our study was to assess the impact of obstetrical neuraxial analgesia on the risk of relapse during the first three months post-partum, with a special focus on women who experienced relapses during pregnancy

Methods

We analyzed data of women followed-up prospectively during their pregnancies and at least three months post-partum, collected in the PRIMS and POPARTMUS studies between 1992-1995 and 2005-2012 respectively. The association of neuraxial analgesia with the occurrence of a post-partum relapse was estimated by logistic regression analysis.

Results

Three hundred and eighty nine women were included, 215 from PRIMS and 174 POPARTMUS. One hundred and fifty six women (40%) had a neuraxial analgesia. Overall, 24% experienced a relapse during pregnancy and 25% in the three months post-partum. Women with a post-partum relapse were more likely to have a pregnancy relapses (OR=1.83, p=0.02), independently of the use of neuraxial analgesia. There was no association between neuraxial analgesia and post-partum relapse (OR=1.08, p=0.78). No interaction was found between covariables.

Discussion

Neuraxial analgesia was not associated with an increased risk of post-partum relapses, whatever MS activity during pregnancy. This suggests that neuraxial analgesia can be used safely in women with MS even when they experience a relapse during pregnancy.

Multiple sclerosis (MS) is a chronic disabling disease affecting mainly women in their childbearing years. For many years, pregnancy was not recommended due to possible deleterious effects of pregnancy on MS course. Large prospective studies have now described the influence of pregnancy on MS and provided reassuring data [1]. The rate of relapse decreases during pregnancy, especially in the third trimester, and increases in the first three months post-partum, before returning to the pre-pregnancy rate. Women who experienced relapses in the year before and during pregnancy have a higher risk of post-partum relapses[2-4]. Pregnancy has no negative influence on disability progression. Moreover, obstetrical and fetal outcomes are similar to the general population[5-9].

However, in clinical practice, obstetrical analgesia remains a matter of controversy, especially among anesthesiologists, because of the fear of neurotoxicity of local anesthetics on demyelinated fibers, which might increase pre-existing symptoms, or their potential relationship with subsequent relapses. For both reasons, this issue seems to be of particular concern in women with recent relapses, in whom neuraxial analgesia might be more frequently contra-indicated by anesthesiologists.

The aim of our study was to assess the impact of obstetrical neuraxial analgesia on the risk of relapse during the first three months post-partum, with a special focus on women who experienced relapses during pregnancy.

PATIENTS AND METHODS

Patient's selection and data collection

Patients were identified retrospectively from two prospective studies, PRIMS and POPARTMUS.

The Pregnancy in Multiple Sclerosis (PRIMS) study was the largest observational, prospective study of the natural history of MS during pregnancy and in the following two years[2-3]. This multicenter study included 254 women with MS from 12 European countries, followed during 269 pregnancies between January 1993 and July 1995, in a period when no disease-modifying drugs were available. Women were included if they had MS according to Poser's criteria[10] and were pregnant for at least 4 weeks but less than 36 weeks at time of entry into the study. If a woman had been followed for more than one pregnancy in the study, only the first one that led to a live birth was considered. Finally, 227 pregnancies were included in the analyses.

The Prevention of Post-Partum Relapses with Progestin and Estradiol in Multiple Sclerosis (POPARTMUS) study was a French and Italian multicenter, randomized, placebo-controlled and double-blind phase III clinical trial[11]. It aimed at assessing the efficacy of administration after delivery of high doses of progestin, in combination with endometrial protective doses of estradiol, on post-partum relapses. Women were included if they had MS diagnosed according to McDonald's 2001 criteria[12], with a relapsing-remitting or secondary progressive course, a Disability Status Scale (DSS)[13] lower than 6 and if they were pregnant for less than 36 weeks at entry into the study. Breastfeeding was not allowed in the study, as well as introduction of a disease-modifying treatment in the six months after delivery. Two hundred and two pregnant women were included between June 2005 and October 2011. The primary endpoint was the annualized relapse rate (ARR) in the first 3 months after delivery. As results were negative, without any trends towards a positive or negative effect of the study treatment, we decided to include all patients in the current study (personal data).

Demographic data and data on the course of MS prior to entry in PRIMS and POPARTMUS were recorded retrospectively: age at onset of MS, age at onset of

pregnancy, number of relapses during the year before pregnancy, residual DSS score at onset of pregnancy, dates of relapses during pregnancy prior to entry in the study. Data on pregnancy relapses occurring after inclusion, relapses during the first three months of post-partum, use of neuraxial analgesia and breastfeeding were collected prospectively.

A relapse was defined as the appearance, reappearance or worsening of symptoms of neurological dysfunction lasting more than 24 hours. Fatigue alone was not considered as a relapse. Disability was assessed with Kurtzke's Disability Status Scale (DSS), which is based on data from the neurological examination and patient's ability to walk. Residual neurologic disability was defined as the minimal level of persistent disability recorded on two consecutive examinations at least three months apart, excluding any transient worsening of disability related to relapses.

Neuraxial analgesia was defined as any type of locoregional analgesia used during delivery, including epidural and spinal analgesia, as no difference has been made between the procedures in the data collection of both studies.

For both PRIMS and POPARTMUS, women were included in the present study only if data about use of neuraxial analgesia was available, if the follow-up was at least 3 months post-partum and if they had MS for at least one year prior to conception.

Standard protocol approvals, registration and patient consents

All patients were informed about the design and purpose of the original studies and all gave their informed, written consent to the protocol. Approval was received from the National French ethical committee on human experimentation for the POPARTMUS study in agreement with French law (March 4, 2002) and the Declaration of Helsinki. The POPARTMUS study is registered with ClinicalTrials.gov under the reference

NCT00127075. The PRIMS study did not require such approvals as it was a non-interventional study.

Statistical analysis

Bivariate and multivariate associations between the occurrence of a relapse during the first three months post-partum and age at pregnancy onset, MS duration at pregnancy onset, DSS score at pregnancy onset , the occurrence of a relapse in the year before pregnancy, the occurrence of a relapse during the pregnancy and neuraxial analgesia were investigated using logistic regression analysis. Continuous covariates such as age were categorized by using the median. Statistically significant variables in the univariate analysis, with a conservative p value of 0.20, and clinically relevant variables were included in a multivariate logistic regression model. All statistical analyses were performed using SAS 9.3 software and a p below 0.05 was considered significant.

Assuming that 25% of women would have a post-partum relapse and that this rate could increase up to 40% if women had an neuraxial analgesia, we calculated that a sample of 393 patients would yield a power of 80%, at a significance level of 0.05, to detect an effect of neuraxial analgesia on the occurrence of a post-partum relapse.

RESULTS

Patient's characteristics

Out of 427 eligible patients, 389 women fulfilled the inclusion criteria of the current study and were included in the analysis (215 out of 227 from PRIMS and 174/202 from POPARTMUS). Main demographic and clinical characteristics of the study group are presented in Table 1.

One hundred and fifty six women (40.1%) underwent neuraxial analgesia, noteworthy in a significantly higher proportion in POPARTMUS (66.7%) than in PRIMS (18.6%)

that might reflect the change in clinical practice over time. Ninety-three women (23.9%) experienced a total of 101 relapses during pregnancy (56, 33 and 12 in the first, second and third trimester respectively) and 97 (24.9%) during the first three months post-partum. The percentage of women who experienced a relapse in the post-partum was lower in the most recent study, POPARTMUS (19.5% vs 29.3%, p=0.04). Neuraxial analgesia was performed in 43.0% of women who experienced a relapse during pregnancy compared to 39.2% of those without active disease.

Risk of post-partum relapse in the overall group

Beside the study effect (more post-partum relapses in PRIMS), three clinical factors significantly correlated with the presence of a post-partum relapse in the univariate analysis (Table 2): the number of relapses in the year before pregnancy, the number of relapses during pregnancy and the residual DSS score at pregnancy onset. By contrast, neuraxial analgesia did not correlate (OR=0.85 [0.53-1.36], p=0.49).

In the multivariate analysis, after excluding the EDSS because of its colinearity with relapses (Table 3), only the number of relapses during pregnancy still correlated independently with the presence of a post-partum relapse (OR=1.83 [1.09-3.09], p=0.02), but, again, not neuraxial analgesia (OR=1.08 [0.62-1.89], p=0.78).

Risk of post-partum relapse in the subgroup with active disease during pregnancy

33 women (35.5%) with a relapse during pregnancy experienced at least 1 relapse during the 3 months post-partum period, compared to 64 women (21.6%) without pregnancy relapse (p=0.007). In this subgroup of active disease, neuraxial analgesia did not correlate to the risk of post-partum relapse. There was furthermore no

interaction between neuraxial analgesia and other covariates, noticeably relapses during pregnancy (p=0.65). The frequency of post-partum relapses was 17 (30.4%), 15 (45.4%) and 4 (33.3%) for women with a relapse during the first, second and third trimester of pregnancy respectively. Because of low numbers, we didn't include the timing of relapses during pregnancy in the modeling procedure.

DISCUSSION

Issues related to pregnancy are of great importance in MS, as two third of the patients are women in their childbearing years. The influence of pregnancy on MS has largely been assessed[1-3] and now women are no longer discouraged from considering pregnancy. Neuraxial analgesia in MS remains a matter of debate between neurologists and anesthesiologists in clinical practice, because of the fear of local anesthetic toxicity or neural ischemia that could worsen the neurologic outcome by a « double-crush » phenomenon. Potential medicolegal issues are also of utmost importance in the decision-making process.

In our study, neuraxial analgesia was not associated with an increased risk of post-partum relapse (OR=1.08 [0.62-1.89], p=0.78). The presence of a relapse during pregnancy was the only factor that independently correlated with the occurrence of this post-partum relapse (OR=1.83 [1.09-3.09], p=0.02). In other words, the risk of post-partum relapses strongly correlated with recent disease activity, but not with performing neuraxial analgesia.

This result is in line with previous reports from prospective cohorts of pregnant women with MS. In PRIMS, 42 women had an epidural analgesia, which was not associated with an increased risk of post-partum relapses[2-3]. Similarly, in the Italian pregnancy cohort, 65 out of 349 women underwent epidural analgesia. No correlation was found

with the occurrence of post-partum relapses[14]. Those studies led neurologists to consider that epidural analgesia, or more largely neuraxial analgesia, could be used safely in women with MS[1,15].

Historically, there has been some reluctance to use neuraxial analgesia in MS patients, MS being viewed as a relative contraindication. Literature on this topic is based essentially on old case reports and small retrospective and prospective observational studies, mainly in an obstetrical context. Data on spinal and epidural analgesia are therefore scarce and contradictory. It remains unclear whether there is a difference between those anesthetic techniques in women with MS[16-20] or whether there is a potential dose effect[20]. In 2006, Drake and al.[21] assessed the views of UK consultant obstetric anaesthetists regarding management of women with MS. The majority would perform spinal or epidural anesthesia and analgesia, after consent given by the patient. MS seems no longer seen as a contraindication of epidural or spinal analgesia. However, in our experience, women with pregnancy relapses are often refused obstetrical loco regional analgesia.

One could argue that we are clearly lacking good evidence based on high level studies, but it would probably be considered unethical and unfeasible to conduct a randomized study to assess the effect of neuraxial analgesia in parturient women with MS. At least, a prospective study, designed specifically and powered to address this question, could provide a better level of evidence. In our study, we tried to approach this design by using prospectively collected data and estimating a priori the number of observations for a satisfactory power.

Our study might suffer some methodological limitations. The retrospective use of data from two studies that were not designed to answer our specific question prevented us from knowing the exact procedure used for neuraxial analgesia (spinal or epidural

analgesia), the local anesthetic used and its concentration. An indication bias on the use of neuraxial analgesia might have occurred, including local differences between centers and temporal differences between the two original studies. The combination of two very different studies that were done more than 10 years apart could be questioned, especially when including a therapeutic trial. But demographic characteristics of both studies were similar and representative of MS women considering motherhood: young women with mild disability, no exposure to disease-modifying treatments in any of the studies, at least during pregnancy and in the three months after delivery. Furthermore, there was absolutely no effect, and even no trend, of sexual steroids on clinical and MRI activity in POPARTMUS (unpublished data). The relapse rates in POPARTMUS were overall lower in all the study periods than in PRIMS, which could be interpreted either as a selection of patients with a lower activity in clinical trials or as a persisting effect of previously used disease-modifying treatments in this much recent study[22]. However, this has unlikely influenced the main analysis on the risk of post-partum relapses related to neuraxial analgesia. The other major difference between the studies laid in the percentage of women that underwent neuraxial analgesia, 18.6% in PRIMS vs 66.7% in POPARTMUS. This important change is mainly due to the evolution of medical practice in the general population (in France, the rate of epidural analgesia for vaginal delivery was 37% in 1991, 51% in 1996 and 63% in 2003[23]), but also in MS patients after the publication of the results of PRIMS. Again, this might not have induced a bias in our main analysis.

There are indeed some pathophysiological arguments to explain a potential risk of using anesthetics in MS patients. Local anesthetics have been reported to unmask silent demyelinated plaques when administered systemically[24] or intrathecally[25]. Several oligopeptides with a sodium channel-blocking activity have been found in an

abnormally high concentration in the cerebrospinal fluid of MS patients[26]. These oligopeptides could be responsible for a transient increase in pre-existing symptoms associated with MS, such as weakness and hypoesthesia, by shifting the steady-state inactivation curve of the sodium channels to more negative potentials therefore inducing a partial conduction block in demyelinated areas. Those physiological properties of oligopeptides are also shared by many local anesthetics[27]. Moreover, demyelination is thought to render the spinal cord more susceptible to a direct neurotoxic effect of local anesthetics.

We clearly miss evidence from a prospective study, collecting detailed information not only on the type of analgesia (route, dose and drug) but also on clinical and MRI parameters (type of symptoms, level of certainty of relapses, localization of the MS lesions, especially in the spinal cord).

Counseling women with MS about pregnancy is part of everyday clinical practice of neurologists. Issues about the safety of neuraxial analgesia for management of obstetrical pain are of great importance. Our study provides additional arguments towards the harmlessness of neuraxial analgesia in parturient women with MS, whatever MS activity during pregnancy. It is important to inform MS women that the post-partum period is associated with a greater risk of relapse, which is closely related to the pregnancy disease activity, but not to the use of locoregional analgesia at the time of delivery. The patient should be actively engaged in the discussion about the choice of the anesthetic technique among the available options and give an informed consent, considering the potential medicolegal implications.

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Table 1: Demographic and clinical characteristics of the cohort

		Original study	
	Overall study cohort	**PRIMS (1992-1995)**	**POPARTMUS (2005-2012)**
	n = 389	**n=215**	**n=174**
Age at MS onset - years			
median [interquartile range]	24.1 [20.8 - 27.6]	24.0 [20.2-27.3]	24.5 [21.4-28.0]
Age at pregnancy onset - years			
median [interquartile range]	31.4 [28.4 - 34.2]	30.7 [27.9-33.1]	32.5 [29.0-35.5]
MS duration at pregnancy onset - years			
median [interquartile range]	5.7 [3.1 - 9.3]	5.3 [2.9-9.0]	6.1 [3.6-9.7]
DSS score at pregnancy onset - n (%)			
< 3	324 (83.%)	179 (83,3%)	145 (83.3%)
≥ 3	56 (14.4%)	32 (14.9%)	24 (13.8%)
Unknown	9 (2.3%)	4 (1.8%)	5 (2.9%)
Relapses in the year before pregnancy			
Yes	129 (33.2%)	100 (46.5%)	29 (16.7%)
No	260 (66.8%)	115 (53.5%)	145 (83.3%)
Relapses during pregnancy			
Yes	93 (23.9%)	60 (27.9%)	33 (19.0%)
No	296 (76.1%)	155 (72.1%)	141 (81.0%)
Relapses during the first 3-month post-partum			
Yes	97 (24.9%)	63 (29.3%)	34 (19.5%)
No	292 (75.1%)	152 (70.7%)	140 (80.5%)
Neuraxial analgesia			
Yes	156 (40.1%)	40 (18.6%)	116 (66.7%)
No	233 (59.9%	175 (81.4%)	58 (33.3%)
Breastfeeding			
Yes	111 (28.5%)	111 (51.6%)	0
No	250 (64.3%)	76 (35.3%)	174 (100%)
Unknown	28 (7.2%)	28 (13.0%)	0

MS= Multiple Sclerosis; DSS= Disability Status Scale

Table 2: Indicators of the occurrence of a relapse in the first 3-month post-partum period - univariate logistic regression analysis

	Post-partum relapses			
	No	**Yes**	**Odds-ratio [95% CI]**	**p value**
Neuraxial analgesia				
Yes	120 (76.9%)	36 (23.1%)	0.85 [0.53 - 1.36]	0.49
No	172 (73.8%)	61 (26.2%)	1	
Relapses during pregnancy				
Yes	60 (64.5%)	33 (35.5%)	2.0 [1.20 - 3.31]	0.007
No	232 (78.4%)	64 (21.6%)	1	
Relapses in the year before pregnancy				
Yes	86 (66.6%)	43 (33.3%)	1.80 [1.12 - 2.89]	0.002
No	210 (80.8%)	50 (19.2%)	1	
Age at pregnancy onset				
< 31 years	156 (74.6%)	53 (25.4%)	1	0.83
≥ 31 years	136 (75.6%)	44 (24.4%)	0.95 [0.60 - 1.51]	
MS duration at pregnancy onset - years				
	5.7 [3.2-9.2]	5.9 [3.0-9.5]	1.00 [0.95 - 1.06]	0.96
DSS score at pregnancy onset				
< 3	256 (79.0%)	68 (21.0%)	1	
≥ 3	29 (51.8%)	27 (48.2%)	3.5 [1.95 - 6.31]	<0.001
Unknown	7	2	1.08 [0.22 - 5.30]	0.93
Original study				
PRIMS	152 (70.7%)	63 (29.3%)	1	0.03
POPARTMUS	140 (80.5%)	34 (19.5%)	0.59 [0.36 - 0.94]	

MS= Multiple Sclerosis; DSS= Disability Status Scale; CI= Confidence Interval

Table 3: Indicators of the occurrence of a relapse in the first 3-month post-partum period - multivariate logistic regression analysis

	Post-partum relapses		
	Odds-ratio	**95% CI**	**p value**
Neuraxial analgesia			
No	1		
Yes	1.08	[0.62-1.89]	0.78
Relapses during pregnancy			
No	1		
Yes	1.83	[1.09-3.09]	0.02
Relapses in the year before pregnancy			
No	1		
Yes	1.52	[0.91-2.52]	0.11
Age at pregnancy onset			
< 31 years	1		
≥ 31 years	0.87	[0.53-1.42]	0.58
MS duration at pregnancy onset - years			
	1.02	[0.96-1.08]	0.57
Original study			
PRIMS	1		
POPARTMUS	0.65	[0,36-1,15]	0.14

MS= Multiple Sclerosis; CI= Confidence Interval

APPENDIX – List of investigators

For the PRIMS study

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