Abstract

Circadian variation in biological rhythms has been identified as affecting both labour pain and the pharmacological properties of analgesics. In the context of pain, there is also a growing body of evidence suggesting the importance of adult attachment. The purpose of this study was to examine whether labour pain, analgesic consumption and pharmacological effect are significantly affected by the time of day, and to analyse whether this circadian variation is influenced by women's attachment style. This prospective observational study included a sample of 81 pregnant women receiving patient-controlled epidural analgesia (PCEA). Attachment was assessed with the Adult Attachment Scale – Revised (AAS-R). The perceived intensity of labour pain in the early stage of labour (3 cm of cervical dilatation and before the administration of PCEA) was measured using a visual analogue scale (VAS). Pain was also indirectly assessed by measuring the consumption of anaesthetics. The latency period and the duration of effect were recorded for a chronopharmacology characterisation. Pain, as assessed with the VAS, was significantly higher in the night-time group than in the daytime group. An insecure attachment style was significantly associated with greater labour pain at 3 cm of cervical dilatation ($p < 0.001$) and before the beginning of analgesia ($p < 0.001$) as well as with higher analgesic consumption and lower pharmacological efficacy ($p < 0.05$). The time of day was significantly associated with the pharmacological effect: the latency period was longer at night, and the duration of the pharmacological effect was longer during the daytime. The interaction between time of day and attachment style was not significant for any of the study variables. Our results provide evidence of the importance of circadian variation in studying labour pain and the pharmacological effect of labour analgesia involving epidural blockage with a PCEA regimen. Moreover, although there was no evidence that attachment style influenced the circadian variation, these data emphasise that insecure attachment patterns are a risk factor for greater labour pain and analgesic consumption, which should be considered in pain management approaches.

Introduction

Chronobiology examines biological rhythms in living systems, whatever their level of organisation. The biochronometrical system is organised hierarchically to ensure its internal synchronisation, but environmental factors also contribute to external synchronisation (Aréchiga, 1993). In human beings, given their complexity, this synchronisation leads to a preponderance of socio-relational *zeitgebers* over natural *zeitgebers*, suggesting an association between psychological variables and individual differences in the organisation of basal circadian rhythms (Adam & Gunnar, 2001).

During labour, rhythmic oscillations in uterine activity and pain have been observed; despite being independent, both exhibit nocturnal acrophases (Aya et al., 2004; Desai et al., 2009; Moore et al., 1994; Zahn & Hattensperger, 1993). For example, in some studies (e.g., Aya et al., 2004; Desai et al., 2009), women reported higher pain during the dark phase (scotoperiod) than during the light phase (photoperiod); however, other studies have not found such an association (Debon et al., 2002; Pan et al., 2005).

Along with the periodic oscillations of pain, it is important to consider the chronopharmacology of analgesics. Opioids and local anaesthetics used for labour analgesia have been shown to exhibit circadian variations, whether administered epidurally or intrathecally (Chassard et al., 2007). However, to the best of our knowledge, no studies have examined the circadian variation of the latency period and the duration of effect of epidural techniques, such as patient-controlled epidural analgesia (PCEA). In other contexts of labour analgesia, Debon et al. (2002) showed that epidural ropivacaine had a longer duration of effect in the photoperiod, with a maximum intra-day variation between groups of 28%. Regarding intrathecal opioids, Pan et al. (2005) found a greater duration of effect of fentanyl in the photoperiod, accounting for a 27% difference over the scotoperiod. Debon et al. (2004) also demonstrated a rhythm for sufentanil, with two peaks (one diurnal and one nocturnal); they reported a difference of approximately 30% between the minimum and maximum values of the duration of analgesia (at acrophase and nadir). Similarly, Vieira et al. (2010), using a sequential spinal epidural technique with a combination of fentanyl and bupivacaine, also reported a diurnal pattern in labour analgesia. Yet, other studies have not reported such differences. For example, Scavone et al.

(2010), analysing two periods (light/dark), showed no influence of the time of day of the administration of intrathecal fentanyl and systemic hydromorphone on the duration of analgesia. Similarly, in a study of Shafer et al. (2010), although the duration of analgesia was decreased in the night period, the difference with the other periods was not significant.

These inconsistencies may have been partly caused by different study designs and different data analysis methods as well as the diversity of individual and environmental factors, which should be considered in studies of the chronobiology of pain and analgesic chronopharmacology (Touitou et al., 2010). Moreover, the mixed findings from research on rhythms is partly due to the nature of the experience of pain, whose perception and communication results from multiple synergistic contributions anchored in individual experiences; as such, labour pain is considered a phenomenon of significant individuality (Bonica, 1996). Indeed, the variability of labour pain is affected by demographic and physical variables (Melzack et al., 1984; Hess et al., 2001), the pharmacological management of uterine activity, which is able to increase contractility and pain (Wei et al., 2009) and by psychological dimensions and individual characteristics (Melzack et al., 1984; Saisto & Halmesmaki, 2003). Among the later, a growing body of research has highlighted the relevance of adult attachment in diverse contexts of pain (Meredith et al., 2008; Meredith, 2013).

Labour is a significant part of pregnancy, and it involves the subjective experiences of women, particularly in relation to their attachment figures (Raphael-Leff, 1995). In adults, the attachment system usually requires strong stress-inducing events to be activated (Hinde & Stevenson-Hinde, 1986). Accordingly, because labour is considered an intense physical and emotional experience (Alehagen et al., 2005), it is likely that distinct attachment styles may play a role in the response to pain during childbirth. According to attachment theory, attachment styles can be divided into secure and insecure styles. The latter can be subdivided into preoccupied, fearful and dismissing (Bartholomew & Horowitz, 1991). Insecure attachment styles have been related to poor emotional regulation (Shaver & Mikulincer, 2007) and to higher levels of stress, which may cause the dysregulation of neurohormonal reactivity and of its rhythms (Oskis et al., 2011; Quirin et al., 2008). Furthermore, there is evidence that individual differences in attachment style are related to different expressions of both chronic (Meredith et al., 2008) and experimentally induced pain (Meredith, 2013)

as well as (more recently) labour pain (Costa-Martins et al., 2014a). Specifically, insecure styles have been related to a reduced pain threshold and a lower ability to cope with pain (Meredith et al., 2006b), more negative appraisals of pain (Ciechanowski et al., 2003) and greater pain intensity (Costa-Martins et al., 2014a; MacDonald & Kingsbury, 2006; McWilliams et al., 2000). However, research has produced conflicting findings regarding pain intensity, with some studies reporting no association with attachment style (Ciechanowski et al., 2003; Davies et al., 2009; Meredith et al., 2006a).

In other contexts of clinical research, an association has been found between attachment and basal biological rhythms, such as cortisol patterns (Kidd et al., 2011). These studies are based on the premise that the interactional process responsible for the development of attachment (Bowlby, 1982) is also involved in the circadian organisation of the hypothalamic-pituitary-adrenal (HPA) axis (De Weerth et al., 2003; Quirin et al, 2008) and that these processes tend to be stable over the lifespan. In fact, there is evidence that the neonatal care provided by the caregiver is a significant predictor of the quality of attachment of the child (Zayas et al., 2011); this care functions as a powerful *zeitgeber* during the sensitive period of individual development (De Weerth et al., 2003; Quirin et al,, 2008) and is thus essential for the external synchronisation of the child's circadian pacemakers (Aréchiga, 1993). Accordingly, it is plausible that attachment styles could influence cyclic changes in the psychobiological expression of labour, particularly the reported pain, considering the importance of the behavioural components of attachment in the management of stress-inducing events (Bowlby, 1982).

Therefore, the aim of this study was to examine whether labour pain, analgesic consumption and the pharmacological effect in women undergoing PCEA were significantly affected by the time of day. An additional aim was to examine whether this circadian variation was influenced by the women's attachment style.

Materials and Methods

Participants and procedures

This prospective observational study was conducted in compliance with the Helsinki Declaration. Ethical approval to conduct the study was obtained from the Ethics Committee of the Alfredo da Costa Maternity Hospital (Lisbon, Portugal), and the study was also approved by the

National Commission of Data Protection. All of the participants were informed of the aims of the study, and those who agreed to participate provided written informed consent. The participants received no compensation for their participation in the study.

The general inclusion criteria for the study were as follows: age $\geq$ 18 years; healthy and singleton pregnancy; nulliparous or parous (up to a third pregnancy); absence of obstetric indices of probable cephalopelvic disproportion; absence of history of caesarean for dystocia; absence of psychopathological disorders and substance abuse; absence of contraindications to epidural techniques; absence of prior analgesia with opioids; and ASA Physical Status lower than III [according to the Physical Status Classification System of the American Society of Anesthesiologists (ASA)].

The sample collection occurred between April 2010 and November 2011. A combined convenience and consecutive sampling approach was used. Women were recruited in the general obstetrics appointment of the Maternity hospital on the basis of the researchers' convenience; however, when the research team was present, women were consecutively recruited in an effort to obtain a better representation of the pregnant population. The participants were assessed at three different times: once in the third trimester of pregnancy (26 weeks or more) and twice during labour. In the first assessment, data were obtained regarding sociodemographic and obstetric-gynaecological factors, and the participants completed the Adult Attachment Scale – Revised (AAS-R). The second and third assessments occurred during labour, before and after the administration of the PCEA protocol, and included the collection of data regarding labour, delivery, the newborn's weight and Apgar score, analgesic technique, pain assessment and pharmacological effect.

Of the 132 pregnant women who agreed to participate in the study, 51 were excluded because they did not complete all of the phases of the study (completion rate = 61.4%). Forty-seven women were excluded because of antenatal assessment omissions (e.g., incomplete sociodemographic, psychometric or biological data), and four were excluded because of the interruption of the analgesic protocol during labour. Thus, the final sample consisted of 81 pregnant women. Women who were excluded from the analyses were more likely to be nulliparous, $\chi^2(1) = 4.31$; $p = 0.038$; Cramer's $V =$

0.18 (69.6% vs. 50.6%) and to report lower attachment anxiety scores, $t(125) = -3.06$, $p = 0.003$,

Cohen's $d = 0.57$ (mean $\pm$ SD $= 2.21 \pm 0.72$ vs. mean $\pm$ SD $= 2.66 \pm 0.84$).

Analgesic technique

The standard PCEA protocol adopted by the institution (ropivacaine 0.6 mg.ml^{-1} plus

sufentanil 0.5 μg.ml^{-1}) was administered to all of the participants at their request and during the first

stage of labour (cervical dilatation 3-4 cm). Based on women's height, after an initial dose (10-12 ml),

the epidural catheter was connected to an infusion pump (Smart Pump CADD®-SOLIS, Smiths

Medical MD, Inc., St. Paul, MN, USA) programmed for a background infusion of 3 ml.h^{-1}, a 5-ml

patient-controlled bolus, a lockout of 15 min, and an hourly limit of 20 ml.h^{-1}. This regimen was

maintained in both the early and later stages of labour. Parturients who experienced inadequate

analgesia during the early stages of labour received supplemental doses, varying from 6-8 ml or 8-10

ml, of a solution of ropivacaine 0.06% (without sufentanil). During the second stage of labour,

whenever necessary, a perineal dose of 6-8 ml of the same solution was administered, according to the

same height intervals. All of the procedures were performed by an anaesthesiologist on the

research/clinical team.

After epidural analgesia was established, and according to the institutional protocol, all of the

women received an oxytocin infusion (10 U.1000 ml^{-1}), with an initial dose of 4 mU.min^{-1} and

increments of 4-5 mU.min^{-1} every 2 h, up to a maximum dose of 15 mU.min^{-1}, adjusted to ensure a

mean progression of cervical dilatation of 1 cm.h^{-1}.

After the PCEA, the women's arterial blood pressure, heart rate, sensory block level (loss of

sensation to cold) and motor block were periodically monitored. During labour, the monitoring also

included tocodynamometry and continuous foetal heart rate. The labour progress was measured at

regular intervals by staff external to the research team.

Measures

Sociodemographic and clinical information

Sociodemographic data (age, education), obstetric-gynaecological history, physical variables

[pre-pregnancy body mass index (BMI), parity, dysmenorrhoea, and menstrual low back pain] and

data about childbirth preparation classes were gathered during an interview conducted in the third

trimester of pregnancy. Additional data were collected during the second and third assessments, including cervical dilatation at the beginning of analgesia and the use of oxytocin before analgesia (pharmacological induction of labour). After birth, the newborn's weight and Apgar scores at 1 and 5 minutes were also collected.

Chronobiological indicators of pain and pharmacotherapy were also recorded. To integrate these indicators with time, the 24 hours of the day were divided into two parts: the photoperiod, corresponding to the phase of light (7:00 h – 18:59 h) and the scotoperiod, corresponding to the dark phase (19:00 h – 6:59 h). Due to the seasonal variation in the photic information that occurred during the study, these divisions were adjusted during the summer months: the interval 6:00 h – 19:59 h was considered the photoperiod, and the interval 20:00 h – 05:59 h was considered the scotoperiod. In the winter months, the interval 08:00 h – 17:59 h was considered the photoperiod, and the interval 18:00 h –7:59 h was considered the scotoperiod.

Adult attachment

Adult attachment was assessed with the Portuguese version of the Adult Attachment Scale – Revised (Canavarro et al., 2006). This scale consists of 18 items scored on a 5-point scale (from 1 = *Not at all characteristic of me* to 5 = *Extremely characteristic of me*) organised into two dimensions (*Anxiety* and *Avoidance*) (Collins, 1996). The participants were assigned to their respective attachment styles based on whether their scores on the attachment-related anxiety and avoidance dimensions were above or below the scale midpoint. Specifically, a participant's attachment style was categorised as secure (lower anxiety and lower avoidance), preoccupied (higher anxiety and lower avoidance), fearful (higher anxiety and higher avoidance), or dismissing (lower anxiety and higher avoidance). In the current sample, Cronbach's alpha values were 0.87 (*Avoidance*) and 0.89 (*Anxiety*).

Assessment of pain

The perceived intensity of labour pain was measured using a visual analogue scale (VAS), with one anchor at 0, which represented "no pain at all," and a second anchor at 100, which represented "the worst pain imaginable." The first measurement was obtained before the administration of the PCEA at 3 cm of cervical dilatation (VAS initial), and the second measurement was obtained at the beginning of analgesia (VAS analgesia) during two consecutive uterine

contractions (mean of the two scores). After the PCEA was initiated, pain was also indirectly assessed by analysing the anaesthetic consumption, which was defined in terms of the average dose per hour. This indicator has also been used as a surrogate measure of pain (Ip et al., 2009) and reflects (indirectly) labour pain because it is determined by the needs of the patient, who is free to administer the required additional analgesia. Local anaesthetic requirements were obtained from the PCEA recordings, and all the records were transcribed as individual reports using the CADD® software (Solis Medication Safety software; Smiths Medical MD, Inc., St. Paul, MN, USA). The timing of rescue doses was recorded by the researchers. The chronobiological categorisation of the VAS scores and analgesic consumption was performed according to the ranges described above.

Assessment of the pharmacological effect

Due to the characteristics of the PCEA, the assessment of the pharmacological effect was limited to the beginning of the technique, i.e., between analgesia induction and when the woman began the use of the PCEA device. For the chronopharmacology characterisation, the latency period and the duration of effect were recorded (in minutes). The latency period corresponded to the time interval between the administration of the first analgesic dose and the stabilisation of the pharmacological effect, identified by the highest level of sensory block. The duration of effect referred to the time interval between the stabilisation of the analgesia and the first self-administration of analgesics, provided by the PCEA device, at the time of the resurgence of the woman's discomfort. The latency period and the duration of effect were characterised as daytime or night-time was made according to the ranges described above. There was no phase change (light/dark) in any of the chronopharmacology values.

Data analysis

The data analyses were conducted using IBM SPSS, version 20.0 (Armonk, NY). Descriptive statistics with means and standard deviations (SD) were reported for continuous variables, and frequencies were reported for categorical variables. An independent samples t-test was used to assess differences in the continuous variables, and a χ^2 analysis was used to identify differences in the categorical variables. The main analysis was a multivariate analysis of covariance (MANCOVA), which was used to test for attachment style and time of day differences (as between-subject factors) in

the different dependent variables (adjusting for potential confounders, identified as those significantly [$p < 0.05$] associated with the dependent variable in univariate analyses). Post hoc power calculations performed for all of the parametric statistical analyses performed with a significance level of 0.05 and power ≥ 0.80 indicated that medium-to-large effects could be detected (Faul et al., 2007). The effect sizes were calculated with Cohen's d for Student's t-test and with Cramer's V for the χ^2 analysis (small effects: Cohen's $d \geq 0.20$, Cramer's $V \geq 0.01$; medium effects: Cohen's $d \geq 0.50$, Cramer's $V \geq 0.03$; large effects: Cohen's $d \geq 0.80$, Cramer's $V \geq 0.05$) (Cohen, 1992).

Results

Participants' characteristics

The study sample consisted of 81 pregnant women in the third trimester of pregnancy (median = 33 weeks), with a mean age of 32.07 (range: 19-45) years. All of the women were married or cohabiting, and the majority had completed secondary ($n = 30$; 37%) or higher education ($n = 37$; 45.7%). Most of the parturients had participated in a programme of preparation for birth ($n = 67$; 82.7%) and delivered at 39 weeks ($n = 46$; 56.8%). The participants' sociodemographic and obstetrical-gynaecological characteristics are presented in Table 1. The characteristics of labour analgesia and pharmacological effect are presented in Table 2.

INSERT_TABLE_1

INSERT_TABLE_2

Regarding the time of day, most of the women began labour during the scotoperiod ($n = 48$; 59.3%). No significant differences were found between the women who started labour during the diurnal and nocturnal periods in the sociodemographic, obstetric or newborn characteristics, with the exceptions of age, $t_{(79)} = 2.84$, $p = 0.006$, and oxytocin use before analgesia, $\chi^2(1) = 4.80$, $p = 0.029$, Cramer's $V = 0.24$. Women who started labour during the nocturnal period were younger than those who started labour during the day, and oxytocin was more likely to be used before analgesia during the day (82.4% vs. 59.6%). Therefore, these variables were included as covariates in the multivariate models.

The distribution of the attachment styles of the sample was as follows: 43 women (53.1%) were classified as secure, 29 (35.8%) as fearful, three (3.7%) as preoccupied, and six (7.4%) as

dismissing. Because fewer participants were identified as having dismissing and preoccupied attachment styles, the participants were categorised into two attachment styles: secure and insecure (i.e., preoccupied, fearful and dismissing grouped together). No significant differences were found between the women with secure and insecure attachment styles in the sociodemographic, gynaecological-obstetric or newborn characteristics.

Correlations among study variables

A variety of preliminary analyses were conducted to examine associations between the demographic and obstetrical-gynaecological variables and the dependent variables. Age was positively correlated with VAS analgesia ($r = 0.25$, $p < 0.05$), the hourly consumption of ropivacaine ($r = 0.31$, $p < 0.01$) and sufentanil ($r = 0.31$, $p < 0.01$), and the ratio of PCEA demands/PCEA delivered ($r = 0.33$, $p < 0.05$). No significant correlations were found between the remaining variables.

The correlations between the independent and dependent variables are shown in Table 3. Overall, the scotoperiod was significantly associated with greater pain at 3 cm of cervical dilatation (VAS initial), a longer latency period and a shorter duration of effect. Concerning attachment, an insecure attachment style was significantly correlated with greater pain (as assessed with the VAS) and analgesic consumption, as well as with a longer latency period and a shorter duration of effect.

INSERT_TABLE_3

Time of day, attachment style and labour pain

A MANCOVA was performed with time of day and attachment style as the between-subject factors and the VAS scores as dependent variables; the results showed significant effects of attachment style and time of day on both pain scores. Women with an insecure attachment style and women who started labour during the scotoperiod reported significantly higher scores for labour pain. The interaction effects of attachment style and time of day were not significant. Table 4 displays the means and standard errors (SE) for the associations between the VAS scores and time of day and attachment style.

INSERT_TABLE_4

Time of day, attachment style and local anaesthetic requirements

With respect to analgesic consumption, controlling for pain before the administration of analgesia, the results showed a significant multivariate effect of attachment style [Wilks' $\lambda = 0.82$, $F(3,72) = 5.40$, $p = 0.002$, $\eta_p^2 = 0.18$]. In particular, the analgesic consumption and the ratio of PCEA demands/PCEA delivered were significantly lower among the secure women (Table 4). The effect of time of day [Wilks' $\lambda = 0.95$, $F(3,72) = 1.38$, $p = 0.257$, $\eta_p^2 = 0.05$] and the interaction effect [Wilks' $\lambda = 0.99$, $F(3,72) = 0.13$, $p = 0.940$, $\eta_p^2 = 0.01$] were not significant (Table 5).

INSERT_TABLE_5

Time of day, attachment style and pharmacological effect

Finally, concerning the pharmacological effect and again controlling for pain before the administration of analgesia, the results showed a significant effect of time of day [Wilks' $\lambda = 0.62$, $F(2,73) = 22.34$, $p < 0.001$, $\eta_p^2 = 0.38$]. An inspection of the mean scores showed that the latency period was longer during the scotoperiod and the duration of effect was significantly longer during the photoperiod (Table 4). The main effect of attachment style [Wilks' $\lambda = 0.99$, $F(2,73) = 0.32$, $p = 0.725$, $\eta_p^2 = 0.01$] and the interaction effect [Wilks' $\lambda = 0.97$, $F(2,73) = 0.96$, $p = 0.389$, $\eta_p^2 = 0.03$] were not significant (Table 5).

Discussion

Biological rhythms are present during labour, whether in relation to uterine contractility (Moore et al., 1994; Zahn & Hattensperger, 1993) or pain (Aya et al., 2004); these rhythms are also present during analgesia (Debon et al., 2002, 2004; Desai et al., 2009; Pan et al., 2005). These rhythms depend on external synchronisation, in which the influence of psychological dimensions is also important (Adam & Gunnar, 2001). In this context, associations between attachment and pain have been observed for different types of pain (Meredith et al., 2008; Meredith, 2013), including labour pain (Costa-Martins et al., 2014a, 2014b). Given this background, this study aimed to investigate the effects of attachment style and time of day on labour pain, analgesic consumption and pharmacological effect. This study also aimed to examine how attachment relates to the chronobiology of labour pain and the chronopharmacology of epidural analgesia, being the first to do so.

One of the main findings of this study was that pain scores (as assessed with a VAS) were significantly lower during the photoperiod than in the scotoperiod. This finding may relate to the

possible influence of endogenous analgesic agents, which have a diurnal acrophase, which is particularly evident in β-endorphin, adrenocorticotropic hormone and cortisol (Allolio et al., 1990; Lindow et al., 1996). Furthermore, it is also plausible that this nocturnal acrophase of labour pain may be related to the inhibition of melatonin secretion following the sleep deprivation commonly associated with artificial light stimulation (photo-inhibition) (LeGates et al., 2012). Indeed, melatonin, signalising the dark phase and the final phase of the neuro-hormonal transduction of sensory information, has been shown to exert an important hypnotic-analgesic action (Arendt & Skene, 2005; Naguib et al., 2003). This hypnotic-analgesic action results from a possible interaction of melatonin with the gamma-aminobutyric acid (GABA), the major inhibitory neuromediator of the central nervous system (Golombek et al., 1996), with the opioid receptors in the pineal gland (Govitrapong et al., 2002) or with the binding to their own receptors (Shavali et al., 2005). These findings are consistent with prior research suggesting that labour pain is lower during the day than at night (Aya et al., 2004, Desai et al., 2009). Our study has several methodological similarities with the work of Aya et al. (2004), including controlling for demographic and physical variables in the expression of labour pain; however, those authors only assessed pain at the beginning of analgesia. Thus, our results extend their findings by also assessing pain at 3 cm of cervical dilatation (the transition from the latent phase to the active phase of labour). Indeed, we found greater pain in the scotoperiod, both in the context of a biological indicator, which was common to all the participants (VAS at 3 cm cervical dilation), and at the time point at which the pain exceeded the individual limit of tolerance (VAS analgesia). Considering the possible interference of the artificial induction of labour in the rhythms of pain (Wei et al., 2009), these results are reinforced by those obtained in the multivariate analyses, which showed that the women who started labour during the scotoperiod reported significantly higher scores for labour pain, although they had a lower incidence of oxytocin induction than those started labour during the photoperiod.

As regards the consumption of analgesics, although a higher consumption was found in the scotoperiod, the difference between the photoperiod and the scotoperiod was not significant. This result is surprising primarily because the VAS assessment clearly identified a nocturnal acrophase for pain. A plausible explanation may be the fact that the institutional obstetric guidelines state that epidural analgesia should be systematically followed by oxytocin infusion. Indeed, although the oxytocin

protocol was the same for all of the participants, the rate of infusion was individually adjusted to ensure a medium progression of 1 cm.h^{-1}. This practice may therefore have introduced a confounding factor, given the changes in the rhythm of uterine contractility and, accordingly, in pain intensity (Wei et al., 2009).

Regarding the chronopharmacological profiles, in view of the analgesic technique that was used in this study, we focused on only the first administration of analgesic solution, controlling for the potential effect of prior pain (VAS analgesia). Based on our results, a greater pharmacological efficacy was found during the photoperiod, which was reflected by a shorter latency period and a longer duration of effect. These findings, albeit more easily explained in the context of the intrathecal block, may also be related to the influence of the increase in body temperature on the decline in the pKa of the local anaesthetic (Morf & Schibler, 2013), which therefore decreased the length of the latency period (Kamaya et al., 1983). The consequence of this decrease in the pKa is an increase in the non-ionised form of the local anaesthetic, which enhances its diffusion capacity and thus reduces the onset time of its effect, mainly at the end of the photoperiod. Concerning the duration of effect, although we only focused on two periods of the day (light/dark), our findings are consistent with prior studies (Debon et al., 2002). It should be noted, however, that our study controlled for potential confounders, thus bolstering the significance of our findings. Several mechanisms related to the circadian variations in the pharmacokinetics and pharmacodynamics of anaesthetics contribute to this cyclic pattern of the duration of effect of local anaesthetics (Chassard et al., 2007). This is a significant finding, given the relevance of determining the time dependency of an analgesic so that its effects can be optimised and its toxicity minimised by basing its administration on the circadian pattern of its activity (Touitou et al., 2010).

This study also showed that insecurely attached women reported significantly greater pain both at 3 cm of cervical dilatation and before the administration of PCEA. These results are consistent with prior studies suggesting an association between insecure attachment styles and higher pain intensity (Costa-Martins et al., 2014a; MacDonald & Kingsbury, 2006; McWilliams et al., 2000; Meredith et al., 2006b), thereby supporting attachment insecurity as a significant factor in vulnerability to pain. Additionally, insecurely attached women reported higher analgesic consumption

and a higher ratio of PCEA demands/PCEA delivered, which reinforces the results obtained using the VAS and substantiates the literature suggesting the importance of psychological variables and individual characteristics in the prediction of analgesic consumption (Costa-Martins et al., 2014b; Ip et al., 2009). This higher pain, increased analgesic consumption and higher PCEA demands/PCEA delivered ratio among insecurely attached women may reflect not only these women's lower confidence in the PCEA technique but also their reduced ability to regulate negative emotions (Shaver & Mikulincer, 2007) and to efficiently cope with stressful experiences, such as pain (Meredith et al., 2006b). In the context of the relationship between attachment and pain, our study is the first to report, in addition to the association with direct and indirect expressions of pain, a significant association between insecure attachment and lower analgesic efficacy (longer latency and shorter duration of effect). In this context, it is plausible that an insecure attachment style, which is related to deviations from baseline circadian rhythms, such as changes in the production of cortisol (a true secondary messenger responsible for the internal synchronisation of other rhythms; Balsalobre et al., 2000), can change the pharmacokinetic and pharmacodynamic patterns of anaesthetics. However, it is also to admit a correspondence between the magnitude of pain and the pharmacological action; thus, attachment may be seen as a relevant covariate in pharmacological studies, as significant as prior pain.

As noted above, this is the first study exploring the potential effects of attachment on the rhythms of pain and analgesic chronopharmacology during labour. This study offers preliminary evidence of a connection between insecure attachment and physiological processes: the univariate analysis indicated a significant correlation between attachment style and pharmacological action. However, our results did not reveal a significant interaction between time of day and attachment style on chronobiological patterns of pain nor on chronopharmacological patterns. It is likely that these findings may result, in part, from the sample size; thus, further research with larger samples is warranted. Based on these results, we can only state that women's attachment styles should be considered an important predictor of labour pain; accordingly, they should be considered as a covariate in future studies of the chronobiology of pain.

Some limitations of this study should be acknowledged. First, a nonprobability sampling method was used, and the available participants may not have been representative of the pregnant

population. Second, the sample size may have limited the strength of the conclusions, considering the statistical test that was applied and its power to detect small but potentially important differences. Indeed, post hoc power calculations demonstrated that this sample size only allowed the detection of medium-to-large effects (Faul et al., 2007). Although our findings are potentially relevant, more studies are needed to replicate and extend these findings. Third, adult attachment was assessed using a self-report measure. Because attachment reflects individuals' subjective perceptions of their close relationships, it is possible that the participants were vulnerable to reporting bias. Fourth, the division of the time of day into only two periods did not allow the identification of ultradian rhythms; thus, we only focused on the circadian rhythms related to the difference between light/dark phases. In addition, women whose labour extended beyond two periods were not excluded; therefore, the analgesic induction dose may have influenced the calculations of pharmacological consumption, particularly when the initial stage of the analgesia occurred shortly before the change in the phase of the cycle of day. However, we considered the induction dose when calculating analgesic consumption because when analgesia consists exclusively of an epidural, this initial volume of analgesic solution is crucial to the establishment of the sensory block before the technique continuously proceeds with the PCEA regimen. Fifth, the analgesic solution consisted of a mixture of local anaesthetics and opioids, and the chronopharmacological profile could not distinguish between these two types of drugs. However, other studies have also resorted to composite solutions without compromising the significance of the results (Vieira et al. 2010). Finally, despite the institutional practice establishing that photic stimulation should be minimised at night, it is impossible to exclude that different levels of photic stimulation may have affected the results by producing different levels of photoinhibition of melatonin (LeGates et al., 2012).

Despite these limitations, this study has several strengths and represents an important contribution to the literature. First, this is the first study to examine the combined effect of attachment styles and the rhythms of pain and pharmacotherapy analgesic by PCEA. Second, we considered seasonal variations in photic information when defining the light and dark phases, in accordance with the recognised oscillation of melatonin throughout the year, characterised by a higher peak in winter than in summer (Claustrat et al., 2005). Third, this was an observational study that respected the

principle of non-intrusion during labour; the assessment of pain during labour analgesia was based on accurate records of the PCEA pump. The current devices allow a computerised record of the technique, with accurate data on the timing of administration and doses of drugs, as well as the conditions under which drug administration occurred (ratio of PCEA demands/PCEA delivered), thus allowing studies with more reliable results. Finally, PCEA is linked to a high level of efficiency, which is associated with increased autonomy and satisfaction of women (Vallejo et al., 2007). These aspects are noteworthy in ultra-light dose protocols with lower doses of analgesics, which produce more evidence of individual variability (Boselli et al., 2003). PCEA allows a therapeutic regimen with reduced interference by institutional constraints and, especially, is based on the individual rhythms of nociception, which is fundamental to the study of rhythms.

In summary, this study confirmed the existence of rhythms in pain and labour analgesia, particularly in the context of PCEA, which allows for women's autonomy during childbirth and reduces external influences by inducing a private environment. This study also evidenced the importance of attachment styles in the experience of pain, analgesic consumption and analgesic effects, reinforcing attachment as a promising area of research, with important implications for understanding pain intensity and analgesic consumption during childbirth. In particular, these results suggest that the effective management of pain requires careful attention to the interpersonal characteristics that may account for individual differences in the pain experience, instead of only focusing on the use of pharmacological agents. Finally, although there was no evidence that attachment style influenced circadian variation, our data emphasise that insecure attachment patterns are a risk factor for greater pain, analgesic consumption and lower analgesic efficacy during childbirth, and they therefore should be considered in pain management approaches and in future research on the chronobiology of obstetric analgesia.

Declaration of interest

The authors declare no conflicts of interest related to this manuscript.

References

Adam EK, Gunnar MR. (2001). Relationship functioning and home and work demands predict individual differences in diurnal cortisol patterns in women. Psychoneuroendocrinology. 26:189-208.

Alehagen S, Wijma B, Lundberg U, Wijma K. (2005). Fear, pain and stress hormones during childbirth. J Psychosom Obstet Gynaecol. 2:153-65.

Allolio B, Hoffmann J, Linton EA, et al. (1990). Diurnal salivary cortisol patterns during pregnancy and after delivery: Relationship to plasma corticotrophin-releasing-hormone. Clin Endocrinol (Oxf). 33:279-89.

Aréchiga H. (1993). Circadian rhythms. Curr Opin Neurobiol. 3:1005-10.

Arendt J, Skene DJ. (2005). Melatonin as a chronobiotic. Sleep Med Rev. 9:25-39.

Aya AG, Vialles N, Mangin R, et al. (2004). Chronobiology of labour pain perception: An observational study. Br J Anaesth. 93:451-3.

Balsalobre A, Brown SA, Marcacci L, et al. (2000). Resetting of circadian time in peripheral tissues by glucocorticoid signaling. Science. 289:2344-7.

Bartholomew K, Horowitz LM. (1991). Attachment styles among young adults: A test of a four-category model. J Pers Soc Psychol. 61:226-44.

Bonica JJ. (1996). The nature of pain in parturiation. In Van Zundert A, Ostheimer GW, eds. Pain relief and anesthesia in obstetric. New York: Churchill Livingstone, pp. 19-52.

Boselli E, Debon R, Duflo F, et al. (2003). Ropivacaine 0.15% plus sufentanil 0.5 microg/mL and ropivacaine 0.10% plus sufentanil 0.5 microg/mL are equivalent for patient-controlled epidural analgesia during labor. Anesth Analg. 96:1173-7.

Bowlby J. (1982). Attachment and loss: Vol. 1. Attachment. 2nd ed. New York: Basic Books.

Canavarro MC, Dias P, Lima V. (2006). A avaliação da vinculação do adulto: Uma revisão crítica a propósito da aplicação da Adult Attachment Scale-R (AAS-R) na população portuguesa [Assessment of adult attachment: A critical revision about the application of the Adult Attachment Scale-R (AAS-R) to the Portuguese population]. Psicologia. 20:155-87.

Chassard D, Duflo F, de Queiroz Siqueira M, et al. (2007). Chronobiology and anaesthesia. Curr Opin Anaesthesiol. 20:186-90.

Ciechanowski P, Sullivan M, Jensen M, et al. (2003). The relationship of attachment style to depression, catastrophizing and health care utilization in patients with chronic pain. Pain. 104:627-37.

Claustrat B, Brun J, Chazot G. (2005). The basic physiology and pathophysiology of melatonin. Sleep Med Rev. 9:11-24.

Cohen J. (1992). A power primer. Psychol Bull. 112:155-9.

Collins N. (1996). Working models of attachment: Implications for explanation, emotion, and behavior. J Pers Soc Psychol. 71:810-32.

Costa-Martins JM, Pereira M, Martins H, et al. (2014a). Attachment styles, pain and the consumption of analgesics during labor: A longitudinal observational study. J Pain. Epub ahead of print.

Costa-Martins JM, Pereira M, Martins H, et al. (2014b). The role of maternal attachment in the experience of labour pain: A prospective study. Psychosom Med. Epub ahead of print.

Davies KA, MacFarlane GJ, McBeth J, et al. (2009). Insecure attachment style is associated with chronic widespread pain. Pain. 143:200-5.

De Weerth C, Zijl RH, Buitelaar JK. (2003). Development of cortisol circadian rhythm in infancy. Early Hum Dev. 73:39-52.

Debon R, Boselli E, Guyot R, et al. (2004). Chronopharmacology of intrathecal sufentanil for labor analgesia: Daily variations in duration of action. Anesthesiology. 101:978-82.

Debon R, Chassard D, Duflo F, et al. (2002). Chronobiology of epidural ropivacaine: Variations in the duration of action related to the hour of administration. Anesthesiology. 96:542-5.

Desai S, Leonng SB, Yvonne L, Sia A. (2009). Chronobiology of parturients receiving neuraxial labour analgesia with ropivacaine and fentanyl: A prospective cohort study. Int J Obstet Anesth. 18:43-7.

Faul F, Erdfelder E, Lang AG, Buchner A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 39:175-91.

Golombek DA, Pévet P, Cardinalli DP. (1996). Melatonin effects on behavior: Possible mediation by the central GABAergic system. Neurosci Biobehav Rev. 20:403-12.

Govitrapong, P., Sawlom, S., Ebadi, M. (2002). The presence of delta and mu, but not kappa or ORL(1) receptors in bovine pinealocytes. Brain Res. 951:23-30.

Hess PE, Pratt SD, Lucas TP, et al. (2001). Predictors of breakthrough pain during labor epidural analgesia. Anesth Analg. 93:414-8.

Hinde, R. A., Stevenson-Hinde, J. (1986). Relating childhood relationships to individual characteristics. In Hartup WW, Rubin Z, eds (Eds.). Relationships and development. Hillsdale, NJ: Lawrence Earlbaum Associates, pp. 27-50.

Ip HY, Abrishami A, Peng PW, et al. (2009). Predictors of postoperative pain and analgesic consumption: A qualitative systematic review. Anesthesiology. 111:657-77.

Kamaya H, Hayes JJ Jr., Ueda I. (1983). Dissociation constants of local anesthetics and their temperature dependence. Anesth Analg. 62:1025–30.

Kidd T, Hamer M, Steptoe A. (2011). Examining the association between adult attachment style and cortisol responses to acute stress. Psychoneuroendocrinology. 36:771-9.

LeGates TA, Altimus CM, Wang H, et al. (2012). Aberrant light directly impairs mood and learning through melanopsin-expressing neurons. Nature. 491:594-8.

Lindow SW, Newham A, Hendricks MS, et al. (1996). The 24-hour rhythm of oxytocin and β-endorphin secretion in human pregnancy. Clin Endocrinol (Oxf). 45:443-6.

MacDonald G, Kingsbury R. (2006). Does physical pain augment anxious attachment? J Soc Pers Relat. 23:291-304.

McWilliams LA, Cox BJ, Enns MW. (2000). Impact of adult attachment styles on pain and disability associated with arthritis in a nationally representative sample. Clin J Pain. 16:360-4.

Melzack R, Kinch R, Dobkin P, et al. (1984). Severity of labour pain: Influence of physical as well as psychologic variables. Can Med Assoc J. 130:579-84.

Meredith P. (2013). A review of the evidence regarding associations between attachment theory and experimentally induced pain. Curr Pain Headache Rep. 17:326.

Meredith P, Ownsworth T, Strong J. (2008). A review of the evidence linking adult attachment theory and chronic pain: Presenting a conceptual model. Clin Psychol Rev. 28:407-29.

Meredith P, Strong J, Feeney JA. (2006a). Adult attachment, anxiety, and pain self-efficacy as predictors of pain intensity and disability. Pain. 123:146-54.

Meredith P, Strong J, Feeney JA. (2006b). The relationship of adult attachment to emotion, catastrophizing, control, threshold and tolerance, in experimentally-induced pain. Pain. 120:44-52.

Moore TR, Iams JD, Creasy RK, et al. (1994). Diurnal and gestational patterns of uterine activity in normal human pregnancy. Obstet Gynecol. 83:517-23.

Morf J, Schibler U. (2013). Body temperature cycles: Gatekeepers of circadian clocks. Cell Cycle. 12:539-40.

Naguib M, Hammond DL, Schmid PG. 3rd, et al. (2003). Pharmacological effects of intravenous melatonin: Comparative studies with thiopental and propofol. Br J Anaesth. 90:504-7.

Oskis A, Loveday C, Hucklebridge F, et al. (2011). Anxious attachment style and salivary cortisol dysregulation in healthy female children and adolescents. J Child Psychol Psychiatry. 52:111-8.

Pan PH, Lee S, Harris L. (2005). Chronobiology of subarachnoid fentanyl for labor analgesia. Anesthesiology. 103:454-6.

Quirin M, Pruessner JC, Kuhl J. (2008). HPA system regulation and adult attachment anxiety: individual differences in reactive and awakening cortisol. Psychoneuroendocrinology. 33:581-90.

Raphael-Leff J. (1995). Pregnancy: The Inside Story. London: Jason Aronson Inc.

Saisto T, Halmesmäki E. (2003). Fear of childbirth: A neglected dilemma. Acta Obstet Gynecol Scand. 82:201-8.

Scavone BM, McCarthy RJ, Wong CA, Sullivan JT. (2010). The influence of time of day of administration on duration of opioid labor analgesia. Anesth Analg. 111:986-91.

Shafer SL, Lemmer B, Boselli E, et al. (2010). Pitfalls in chronobiology: A suggested analysis using intrathecal bupivacaine analgesia as an example. Anesth Analg. 111:980-5.

Shavali S, Ho B, Govitrapong P, et al. (2005). Melatonin exerts its analgesic actions not by binding to opioid receptors subtypes but by increasing the release of beta-endorphin an endogenous opioid. Brain Res Bull. 64:471-9.

Shaver PR, Mikulincer M. (2007). Adult attachment strategies and the regulation of emotion. In Gross JJ, ed. Handbook of emotion regulation. New York: Guilford Press, pp. 446-65.

Touitou Y, Dispersyn G, Pain L. (2010). Labor pain, analgesia, and chronobiology: What factor matters? Anesth Analg. 111:838-40.

Vallejo MC, Ramesh V, Phelps AL, Sah N. (2007). Epidural labor analgesia: Continuous infusion versus patient-controlled epidural analgesia with background infusion versus without a background infusion. J Pain. 8:970-5.

Vieira WS, Hidalgo MP, Torres IS, Caumo W. (2010). Biological rhythms of spinal-epidural labor analgesia. Chronobiol Int. 27: 865-78.

Wei SQ, Luo ZC, Xu H, Fraser WD. (2009). The effect of early oxytocin augmentation in labor: A meta-analysis. Obstet Gynecol. 114: 641-9.

Zahn V, Hattensperger W. (1993). Circadian rhythm of pregnancy contractions. Z Geburtshilfe Perinatol. 197:1-10.

Zayas V, Mischel W, Shoda Y, Aber JL. (2011). Roots of adult attachment: Maternal caregiving at 18 months predicts adult peer and partner attachment. Soc Psychol Personal Sci. 2:289-97.

Table 1. Participants' sociodemographic, clinical and obstetrical characteristics ($N = 81$)

	n (%)
Nulliparous	41 (50.6)
Low back pain	22 (27.2)
Dysmenorrhoea	10 (12.3)
Oxytocin use before analgesia	56 (69.1)
Mode of delivery	
Vaginal	57 (70.4)
Instrumental	13 (16.0)
Cesarean	11 (13.6)
Apgar score < 7	
At 1 min	8 (9.9)
At 5 min	2 (2.5)
	Mean (SD)
Age (years)	32.07 (5.09)
Body mass index (pre-pregnancy) (kg.m^{-2})	24.47 (3.77)
Gestational age at delivery (weeks)	39.12 (0.68)
Cervical dilatation before analgesia (cm)	3.48 (0.50)
Newborn birthweight (gr)	3190.89 (343.14)

Table 2. Characteristics of labour analgesia and pharmacological effect ($N = 81$)

	Mean (SD)
Duration of analgesia (min)	328.07 (177.35)
Total volume of analgesic solution (ml)	57.29 (28.83)
Total dose of ropivacaine (mg)	34.37 (17.30)
Hourly dose of ropivacaine (mg.h^{-1})	6.67 (2.00)
Total dose of sufentanil (μg)	26.99 (11.53)
Hourly dose of sufentanil (μg.h^{-1})	5.36 (1.74)
Number of boluses	5.12 (3.21)
Ratio PCEA demands/ PCEA delivered	2.10 (0.70)
Latency period (min)	13.33 (2.86)
Duration of effect (min)	44.51 (25.34)
	n (%)
Patients requesting rescue analgesia	11 (13.6)
0-1 supplemental boluses during first stage	5 (6.2)
≥ 2 supplemental boluses during first stage	5 (6.2)
0-1 supplemental boluses during second stage	7 (8.6)
≥ 2 supplemental boluses during second stage	0 (0.0)

Table 3. Correlations between study variables

Variables	VAS initial (mm)	VAS analgesia (mm)	Hourly dose of ropivacaine (mg.h^{-1})	Hourly dose of sufentanil (µg.h^{-1})	Ratio PCEA demands/ PCEA delivered	Latency period (min)	Duration of effect (min)
VAS initial (mm)	-						
VAS analgesia (mm)	0.65***	-					
Hourly doses of ropivacaine (mg.h^{-1})	0.22*	0.40***	-				
Hourly doses of sufentanil (µg.h^{-1})	0.14	0.30**	0.96***	-			
Ratio PCEA demands/PCEA delivered	0.41***	0.52***	0.50***	0.43***	-		
Latency period (min)	0.44***	0.60***	0.19	0.12	0.14	-	
Duration of effect (min)	-0.47***	-0.68***	-0.42***	-0.35**	-0.29**	-0.49***	-
Time of day	0.34**	0.17	0.07	0.07	-0.08	0.45***	-0.50***
Attachment style	-0.43***	-0.52***	-0.48***	-0.40***	-0.51***	-0.26*	0.26*

Note: Time of day (0 = Photoperiod, 1 = Scotoperiod); Attachment style (0 = Insecure, 1 = Secure).

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 4. Mean scores and SE on pain scores, analgesic consumption and pharmacological effect, by time of day and attachment style (adjusted for covariates)

	Secure ($n = 43$)		Insecure ($n = 38$)	
	Photoperiod	Scotoperiod	Photoperiod	Scotoperiod
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Pain				
VAS initial (mm)	49.84 (0.40)	66.58 (0.37)	63.90 (0.44)	81.77 (0.36)
VAS analgesia (mm)	75.99 (0.26)	79.97 (0.22)	85.30 (0.27)	94.43 (0.23)
Analgesic consumption				
Hourly dose of ropivacaine (mg.h^{-1})	5.66 (0.45)	6.19 (0.36)	7.24 (0.44)	7.60 (0.42)
Hourly dose of sufentanil (μg.h^{-1})	4.52 (0.41)	5.04 (0.33)	5.68 (0.40)	6.15 (0.38)
Ratio PCEA demands/PCEA delivered	1.97 (0.15)	1.87 (0.12)	2.46 (0.14)	2.22 (0.14)
Pharmacological effect				
Latency period (min)	12.16 (0.55)	14.19 (0.45)	11.94 (0.54)	14.24 (0.51)
Duration of effect (min)	56.68 (4.16)	32.94 (3.35)	54.80 (4.05)	41.29 (3.86)

Table 5. Attachment style and time of day differences including the interaction effect of time of day x attachment style on pain scores, analgesic consumption and pharmacological effect (adjusted for covariates)

	Time of day			Attachment style			Time of day x attachment style		
	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
Pain									
VAS initial	17.24	< 0.001	0.19	14.32	< 0.001	0.16	0.02	0.883	0.00
VAS analgesia	6.86	0.011	0.08	23.91	< 0.001	0.24	1.12	0.293	0.02
Analgesic consumption									
Hourly dose of ropivacaine	1.11	0.296	0.02	10.82	0.002	0.13	0.04	0.837	0.00
Hourly dose of sufentanil	1.62	0.207	0.02	7.33	0.008	0.09	0.01	0.940	0.00
Ratio PCEA demands/PCEA delivered	1.51	0.222	0.02	8.12	0.006	0.10	0.26	0.610	0.00
Pharmacological effect									
Latency period	17.04	< 0.001	0.19	0.02	0.882	0.00	0.08	0.783	0.00
Duration of effect	22.42	< 0.001	0.23	0.59	0.444	0.01	1.93	0.169	0.03