

## Original Article

# Effect of Pethidine Administered During the First Stage of Labor on the Infants

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### Abstract

**Background:** Pethidine is used for pain relief in the first stage of labour in many countries, and it is accepted as standard obstetric management in Turkey. This study is conducted to determine the effect of analgesics that are administered to mothers intramuscularly at the first stage of the labor on health state of the infants.

**Methods:** This cross-sectional controlled study was conducted between 1 June 2010 and 30 May 2011 in the Zeynep Kamil Maternity and Children's Teaching Hospital of the Republic of Turkey Ministry of Health Istanbul, Turkey. The population of the study consists of 1550 mothers who had normal labor and their infants, the sample consists of 245 mothers and their infants who are suitable for the criteria of sample. Sample size, was selected are on the same dates and normal mothers who gave birth were identified at random from among. Their babies were observed in terms of health condition both during the labor process and the first 24 hours after the birth. Then mothers' files were reviewed and determined in terms of administered analgesics during the first stage of labor. Pethidine the case group was comprised of mothers and babies and Pethidine not applied as the control group of mothers and babies.

**Results:** Case and control group mothers were similar in terms of demographic and obstetric features. The average apgar scores of the case group infants were found to be significantly lower than the control group infants during the 1st to 5th minutes after their birth. The sucking and rooting reflexes of infants in the case group were unsatisfactory when compared to the control group.

**Conclusions:** Intramuscular Pethidine analgesia during the first stage of labor negatively impacted the apgar scores of newborns.

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**Key Words:** Analgesic, Newborn, Healthstate, Labor, Pethidine, Apgar Score

### Background

For many women, birth is a severely painful experience. Research reveals that birth is one of the most known sources of physical pain. There have been yet many controversies about these techniques, also many physicians believe labor pain is natural and essential in natural birth (Wee, et al., 2011).

Drug administered in control of labor pain are divided in two groups, systemic and local. Intramuscular administration of Pethidine to the mother during the first stage of labor is one of

the most common methods of analgesics (Bricker, & Lavender, 2002; Sosa, 2006).

Pethidine also has a number of side effects on both the mother and the neonate which make it a less than ideal choice for labour analgesia. It crosses the placenta and can cause reduced fetal heart rate variability and fewer heart rate accelerations (Solt, et al., 2002).

Effects on the neonate include respiratory depression, impaired feeding and crying (Nissen, et al., 1997; Ransjo-Arvidson, et al., 2001).

Observational studies have found negative effects on newborn infants and the following negative newborn effects have been reported; low apgar scores (Gerhardt, et al., 1977; Shnider, & Moya, 1964; Fairlie, et al., 1999; Reynolds, 2010), neonatal respiratory depression (Taylor, et al., 1955; Hamza, et al., 1989), acidosis at birth (Sosa, 2006), decreased neonatal alertness and lower neurobehavioral alertness (Hodgkinson, et al., 1978). Newborn depression has been associated not only with the use of pethidine, but also with maternal administration-birth period of time (Nissen, et al., 1995; Nissen, et al., 1997).

Despite the disadvantages of Pethidine, some researchers concluded that it had no adverse effects on health of the infants (Giannina, et al., 1995; Khooshideh, & Shahriari, 2009; Konefal, et al., 2012; Yousefshahi, et al., 2013), and there are few large studies comparing the relative side effects and effectiveness of different opioids in labour and systematic reviews comparing opioids in labour have suggested a need for well-designed and suitably sized trials of Pethidine versus other opioids (Bricker, & Lavender, 2002; Ullman, et al., 2010).

Therefore, a research of the literature has proven that the results of Pethidine administration to mothers during the birth had proven to be inconclusive, since its effects on the health of the infants during prenatal and postnatal periods had produced different results, which makes us think that a comprehensive study in this area is a necessity.

This study is conducted to determine the effect of analgesics that are administered to mothers intramuscularly at the first stage of the labor on health state of the infants.

### **Methodology**

This cross-sectional designed case-control study was conducted between June 2010 and May 2011 in the Zeynep Kamil Maternity and Children's Teaching Hospital of the Republic of Turkey Ministry of Health Istanbul. Written ethical approval for the study was obtained from the ethical review board of the hospital. The sample size was determined as 231, with 5 % mistake and 90 % confidence interval. Taking into consideration the possibility of the loss of cases, it was decided that 245 mothers should comprise the sample group. Since it was a single blind research, no preferences were made in terms of

the relevant factors for choosing the case and control groups.

The mothers and the infants who were administered Pethidine were included in the case group, and after the monitoring period was over, their case files were consulted, whereas the mothers and the infants who were not given any analgesics were placed in the control group. Consequently, the sample comprised of 245 mothers who gave normal birth and their newborns that fitted the sample criteria; of which 115 were placed in the sample group and 130 into the control group.

To increase the data security and as a measure against any bias, the research was conducted as a single blind research. First, the pregnant women who fit the sample criteria and who wanted to take part in the research were determined. Then, the newborns of the mothers who fit the sample criteria were monitored from the second period of birth, until the 24th hour in terms of sucking skills and overall health. When the monitoring of the newborns was over, whether or not the mother was administered

Pethidine and other data on the mother were recorded onto the mother's files. This way, while the researcher was monitoring the newborns, it was ensured that the evaluation of the newborns was done without the researcher knowing if the mother belonged to the case or control group. The same researcher conducted the monitoring of the infants in both the case and the control groups.

The Criteria Employed in Choosing the Sample Group is as follows: For the mothers to be older than 18 and younger than 35 for the mothers not to have prior health problems that would obstruct normal birth (antepartum hemorrhage, anticoagulant treatment, chronic illness, tumor etc.), for the fetus to be in the cephalic position, for the newborn to have a gestation age of 38 to 42 gestation weeks, for the newborn to have a birth weight of 2500g to 4000g.

In data collection, "Identification Information Form", "Mother Follow-up Form", "Newborn Follow-up Form" were used. The researcher developed all forms based on the literature. The researcher according to opinions, criticism and feedback provided by experts finalized the forms.

The data derived from the research was evaluated by SPSS (Statistical Package for Social Sciences)

for Windows 16.0. During the statistical analysis, the evaluation of the quantitative data was conducted by means of average, student t test and Mann Whitney U test. The evaluation of the qualitative data was done by means of frequency, Yates corrective ki-square test and Fisher. The statistical significance was evaluated at 95 % confidence interval,  $p < 0.05$ .

## Results

It was concluded that the factors that might impact the overall health of the newborn, that is perimeter of the head, body weight and height had no effect ( $p > 0.05$ ). Education, type of pregnancy, abortion and miscarriage rates again had no effect ( $p > 0.05$ ) (Table 1).

When the factors related to the administration of Pethidine to the mothers in the case group was examined, it was found that the birth took place approximately  $168.35 \pm 126.27$  (min: 15 min., max: 750min.) minutes after the administration of Pethidine and that during the Pethidine administration the cervical dilatation was approximately  $4.68 \pm 1.26$  cm (min: 1cm, max: 8cm) (Table 2).

Table 3, covers the factors related to the health of the newborns and the comparison of groups according to the attempts at intervention. The newborns in the case group had the following apgar score at 1st minute and 5th minute (respectively  $p < 0.001$ ;  $p < 0.01$ ), which attests to a significantly lower level.

When the newborns with apgar scores lower than 7 were examined according to the groups; it was discovered that in the case group, the numbers of the newborns at 1st minute who had apgar score under 7 was ( $p < 0.001$ ), which is significantly high, and at 5th minute between case and control groups there existed no statistically significant difference ( $p > 0.05$ ).

It was discovered that in terms of the attempts at resuscitation, between case and control groups there existed no statistically significant difference ( $p > 0.05$ ). However, when compared in terms of the attempts at oxygen inhalation, it was found out that the newborns in the case group required statistically more oxygen application procedures ( $p < 0.001$ ).

Furthermore, the newborns in the group that was administered Pethidine had significantly higher levels of aspiration application ( $p < 0.001$ ). The newborns in the case group needed deep tracheal aspiration attempts of a significantly higher rate than those who were not administered Pethidine ( $p < 0.001$ ). There was no difference among the groups in terms of meconium aspiration development ( $p > 0.05$ ) (Table 3).

Rooting, sucking, catching and moro reflexes of the newborns were evaluated 5 times, at 15th minute, 30th minute, 1st hour, 2nd hour and 24th hour. When the presence of the **Rooting reflex** was evaluated in both groups; it was found that in the case group the rooting reflex of the newborns at 15th minute, 30th minute and 1st hour after the birth were significantly lower (according to all three time spans  $p < 0.001$ ).

At 2nd hour and 24th hour the difference between the groups was not noteworthy ( $p > 0.05$ ; Diagram 1). When the presence of the **Sucking reflex** was evaluated in both groups; it was found that in the case group newborns that had sucking reflex at 15th minute, and 30th minute were significantly lower than the control group ( $p < 0.001$ ).

At the end of the 1st hour, the case group newborns that had sucking reflex were numerically lower than the control group ( $p < 0.05$ ), however, at the 2nd hour and 24th hour the significant difference disappeared ( $p > 0.05$ ; Diagram 1).

When the presence of the **Catching reflex** was evaluated in both infant groups; it was found that in the case group newborns the levels at 15th minute, was found to be significantly lower than the control group ( $p < 0.001$ ), whereas at 30th minute, 1st hour, 2nd hour and 24th hour after the birth, the catching reflex ratio did not statistically differ ( $p > 0.05$ ; Diagram 1).

In terms of the presence of the **Moro reflex**, in the case group at 15th minute, it was significantly lower than the control group ( $p < 0.05$ ), it was discovered that at 30th minute, 1st hour, 2nd hour and 24th hour after the birth, the presence of the moro reflex did not statistically differ ( $p > 0.05$ ) (Diagram 1).

**Table 1: Comparison of the groups in terms of the factors related to the mother and the newborn that might impact the health of the newborn**

<b>Features</b>	<b>Case Group (n: 115) Mean ± SD</b>	<b>Control Group (n:130) Mean ± SD</b>	<b>t/p</b>
<b>Newborn</b>			
Head	34.26± 0.48	34.20± 0.42	0.98/.064
Circumference			
Body Weight	3256.91±366.6	3274.69± 382.06	0.37/.213
Height	50.38± 1.00	50.13± 1.00	1.95/.281
<b>Maternal</b>			
Age	25.05± 4.76	24.95± 4.31	0.17/.865
Body Weight	71.60± 10.27	72.36± 8.64	0.63/.529
Height	160.37± 5.27	160.34 ± 5.73	0.03/.970
	<b>Case Group n (%)</b>	<b>Control Group n (%)</b>	<b>χ<sup>2</sup>/p</b>
<b>Educational Status</b>			
Illiterate	13 (11.3)	16 (12.3)	
Primary Education	75 (65.2)	90 (69.2)	1.25/.739
High School	21 (18.3)	17 (13.1)	
University	6 (5.2)	7 (5.4)	
<b>Parity</b>			
Primipara	75(65.2)	75 (57.7)	1.45/.228
Multipara	40(34.8)	55 (42.3)	
<b>Curettage</b>			
No	5(4.3)	4 (3.1)	-.738*
Yes	110(95.7)	126 (96.9)	
<b>Abortion</b>			
No	12(10.4)	10 (6.2)	0.27/.599**
Yes	103(89.6)	120( 92.3)	

\*During monitoring, since expected value was less than 5, Fisher full \*chi-square test was given.

\*\* During monitoring, because monitored value was less than 25, Yates corrective \*chi-square test was given.

**Table 2: Factors related to the time and duration of Pethidine administration to the mothers in the Case Group**

Pethidine Grup	Min-Max Value	Mean±SD
Injection to Delivery Interval (min)	15-750	168.35±126.27
Cervical Dilatation (cm)	1-8	4.68±1.26 cm

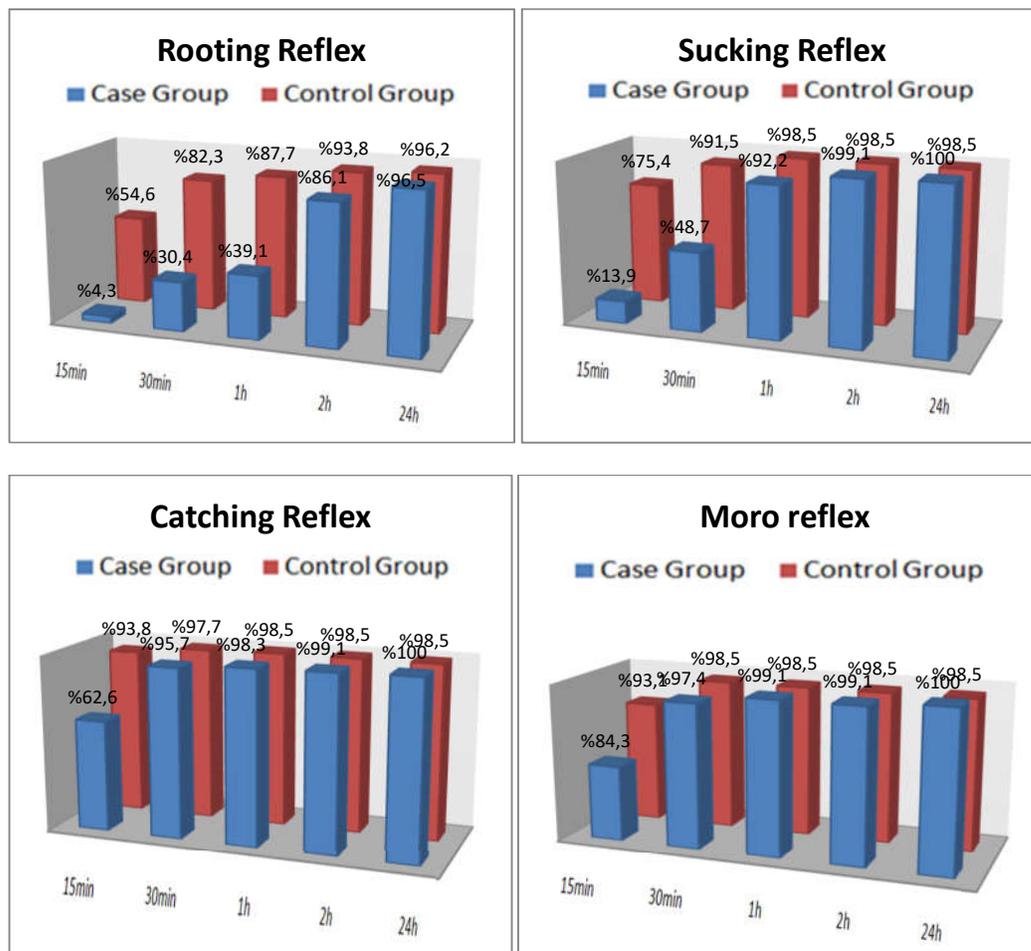
**Table 3: Factors related to the health of the newborns and the comparison of groups according to the attempts at intervention**

Features	Case Group (n: 115) Mean ± SD	Control Group (n: 130) Mean ± SD	t/ p
<b>Apgar Score</b>			
1.min	6.94±1.10	7.50±0.73	4.63/ .000
5.min	8.66±0.65	8.85±0.42	2.61/.008
	<b>n (%)</b>	<b>n (%)</b>	<b>χ<sup>2</sup>/p</b>
<b>Apgar Score Group</b>			
1.min 7 ↓	30 (26.0)	11(8.4)	13.60/.000
5.min 7 ↓	2 (1.7)	0 (0)	2.27/.219**
<b>Resuscitation</b>			
Yes	6 (5.2)	2 (1.5)	-.152*
No	109(94.8)	128(98.5)	
<b>Oxygen Inhalation</b>			
Yes	41(35.7)	17(13.1)	15.98/.000**
No	74(64.3)	113(86.9)	
<b>Decelerations(Fetal Heart Rate)</b>			
None	71(61.8)	116(89.2)	
Early	6 (5.2)	8(6.2)	33.59/.000
Late	38(33.0)	6(4.6)	
<b>Attempt to Aspiration</b>			
None	46(40.0)	100(76.9)	
Mouth-Nose A.	49(42.6)	18(13.8)	36.46/.000**
Deep Tracheal A.	20(17.4)	12(9.3)	
<b>Meconium Aspiration</b>			
Yes	6 (5.2)	11(8.5)	
No	109(94.8)	119(91.5)	0.55/0.456**

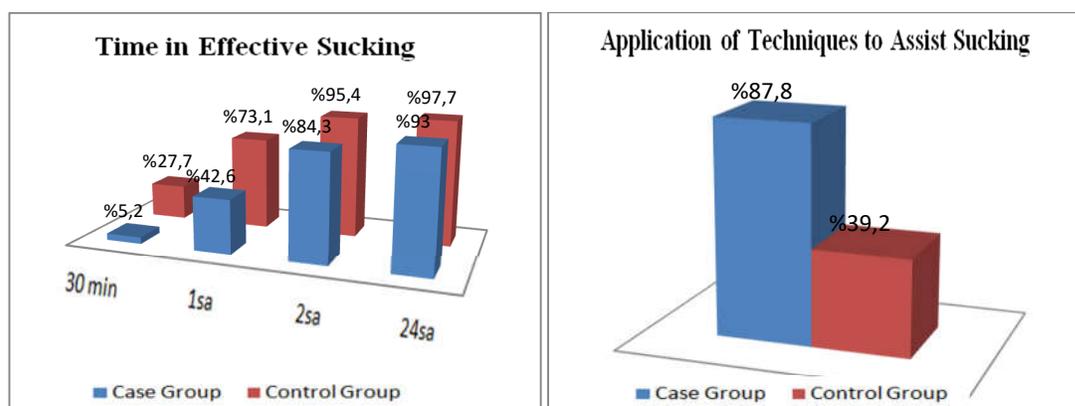
\*During monitoring, since expected value was less than 5, Fisher full \*chi-square test was given.

\*\* During monitoring, because monitored value was less than 25, Yates corrective \*chi-square test was given.

**Diagram 1: Comparison of the appearance time of newborn reflexes according to the groups**



**Diagram 2: Comparison of the newborns in both groups in terms of the time by which they engaged in effective sucking**



## Discussion

The data derived from this research suggests that either in the case or control groups, there were not any pre-existing factors related to the mothers or the newborns that could effect the overall health of the newborns ( $p>0.05$ , Table 1). When the time and period of Pethidine administration to mothers in the case group was examined, it was revealed that approximately 168 minutes after Pethidine administration (approximately 2 to 3 hours) the birth took place.

The research conducted by Nissen et. al. on 13 pregnant women, in which they examined the relationship between the period that elapsed between Pethidine administration and birth, and its effect on the newborns; the results were evaluated in two groups, namely a short period between Pethidine administration and birth (1 to 5 hours) and a long period between Pethidine administration and birth (8 to 9 hours). It was discovered that the newborns of the pregnant women who gave birth after a short period of Pethidine administration (1 to 5 hours), had had their mouth and lip motions and sucking skills repressed, thus arguing that the newborns were affected adversely (Nissen, et al., 1997).

Pethidine reaches its maximum analgesic effect after approximately 40 to 50 minutes of the IM application, passes on to fetal circulation in 90 seconds, and reaches its highest level in blood in 2 to 3 hours (Comart, 2006). The fact that, according to our findings, the birth took place approximately 168 minutes (approximately 2 to 3 hours) after the mothers in the case group were administered Pethidine shows that Pethidine was able to reach its highest level in the blood of the newborns, and similar to the results by Nissen et. al. it has a high potential to affect the newborns (Nissen, et al., 1995).

Furthermore, our research has revealed that Pethidine was administered when the cervical dilatation (min: 1cm, max: 8cm), was approximately  $4.68\pm 1.26$  cm (Table 2). In the research conducted by Khooshideh & Shahriari, 80 pregnant women were administered via IM 50 mg Pethidine, and 80 pregnant women were administered via IM Tramadol, with the result that in both groups the newborns' apgar scores at 1st and 5th minutes were over 7. The researchers have pointed out that in this research they have preferred to administer Pethidine at such a vaginal dilation that the birth will not take place

in a short period (2 to 3 hours before), and by this method they have tried to reduce the possibility of the adverse effects of Pethidine on the newborns (Khooshideh, & Shahriari, 2009).

In our study the apgar scores of the newborns in the case group at 1st and 5th minutes on average were lower, since while 26.0 % of those in the case group, as opposed to 8.4 % of those in the control group had apgar scores below 7 at 1st minute, which amounts to a statistically significant difference. At 5th minute on the other hand, the newborns with apgar scores below 7 were similar in both groups (Table 3). In the research conducted by Fairlie et. al., of the newborns whose mothers were administered Pethidine, the apgar score below 7 at 1st minute were 26.0 %, however at 5th minute only 4.0 % had apgar scores below 7 (Fairlie, et al., 1999). Tsui et al., did not observe any difference in neonatal outcome between groups (Tsui, et al., 2004). Therefore, our results suggest that, similar to the findings of Fairlie et. al., the newborns were affected more during the first few minutes after birth, and that the effect wore off later (Fairlie, et al., 1999).

Although there was no difference among the newborns in terms of attempts at resuscitation and meconium aspiration development frequency, the newborns in the case group needed more oxygen inhalation and deep tracheal aspiration (Table 3). This occurrence must be the result of the fact that Pethidine has the effect of depressing respiration, and that the respiration of the newborns was significantly compromised, and they recovered only by means of interventions of aspiration and oxygen inhalation.

The research conducted by Fienni et. al., in which 20 pregnant women were via IM administered 75 mg of Meperidine, and the respiratory depression of newborns were evaluated, it was concluded that as well as the pH values in the umbilical cord, and the apgar score, the newborns in the group that were administered Meperidine developed respiratory depression (Fienni, et al., 2000). The results of this research supports those of Fienni et. al., Belfrage et. al., Reynolds et al., strengthens the argument that Pethidine results in respiratory depression in newborns (Belfrage, et al., 1981; Fienni, et al., 2000; Reynolds, et al., 2002).

Our research shows that the rooting, sucking, catching and Moro reflexes of the newborns were adversely affected especially during the first few minutes after birth by Pethidine administration to mothers (Diagram 1). Tuckey et al.'s meta-analysis which detailed the IM administered systemic analgesics' effects on the newborns, revealed that the newborns whose mothers were administered analgesics, had their sucking and rooting reflexes suppressed (Tuckey, et al., 2008).

Nissen et al. in their research evaluated the sucking skills of newborns 2 hours after birth; one group comprised of newborns whose mothers were IM administered Pethidine, the other group whose mothers were not given drugs; they have concluded that the newborns of mothers administered Pethidine had their rooting and sucking reflexes suppressed (Nissen, et al., 1995).

Similar to the research results of Tuckey et al., Nissen et al., our research has shown that the newborns of mothers that were administered Pethidine had their reflexes adversely affected during the first few minutes after birth, and that the newborns recovered eventually, but the longest lasting effect was in the sucking and rooting reflexes (Nissen, et al., 1995; Tuckey, et al., 2008). The fact that the newborns whose mothers were administered Pethidine had their sucking and rooting reflexes compromised, especially during the first half hour after birth, made us conclude that they had a high potential of experiencing sucking difficulties in the future, since the initial sucking did not take place during the active phase, when the newborn was most prone to start sucking (Ransjo-Arvidson, et al., 2001).

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### References

- Wee, M.Y., Tuckey, J.P., Thomas, P., Burnard, S. (2011). The IDVIP trial: A two-centre randomised double-blind controlled trial comparing intramuscular diamorphine and intramuscular pethidine for labour analgesia. *BMC Pregnancy Childbirth*, 8, 11-51.
- Bricker, L. & Lavender, T. (2002). Parenteral opioids for labor pain relief: A systematic review. *J Am Obstet Gynecol*, 186, 94-109.
- Sosa, C.G. (2006). Effect of pethidine administered during the first stage of labor on the acid-base status at birth. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 129, 135-139.
- Solt, I., Ganadry, S., Weiner, Z. (2002). The effect of meperidine and promethazine on fetal heart rate indices during the active phase of labor. *Isr Med Assoc J*, 4, 78-180.
- Nissen, E., Widstrom, A.M., Lilja, G., Matthiesen, A.S., Moberg, K.U., Jacobsson, G., et al. (1997). Effects of routinely given pethidine during labour on infants' developing breastfeeding behaviour; Effects of dose-delivery time interval and various concentrations of pethidine/norpethidine in cord plasma. *Acta Paediatrica*, 86(2), 201-8.
- Ransjo-Arvidson, A.B., Matthiesen, A.S., Lilja, G., Nissen, E., Widstrom, A.M., Uvnas-Moberg, K. (2001). Maternal analgesia during labor disturbs newborn behavior: Effects on breastfeeding, temperature, and crying. *Birth*, 28(1), 5-12.
- Gerhardt, T., Bancalari, E., Cohen, H., Macias-Loza, M. (1977). Respiratory depression at birth value of Apgar score and ventilatory measurements in its detection. *J Pediatr*, 90(6), 971-5.
- Shnider, S.M. & Moya, F. (1964). Effects of meperidine on the newborn infant. *Am J Obstet Gynecol*, 89, 1009-15.
- Fairlie, F.M., Marshall, L., Walker, J.J., Elbourne, D. (1999). Intramuscular opioids for maternal pain relief in labour: A randomised controlled trial comparing Pethidine with Diamorphine. *British Journal of Obstetrics and Gynaecology*, 106, 1181-1187.
- Reynolds, F. (2010). The effects of maternal labour analgesia on the fetus. *Best Practice & Research Clinical Obstetrics and Gynaecology*, 24, 289-302.
- Taylor, E.S., Von Fumetti, H., Essig, L.L., Goodman, S.N., Walker, L.C. (1955). The effects of demerol and trichlorethylene on arterial oxygen saturation in the newborn. *Am J Obstet Gynecol*, 69(2), 348-51.
- Hamza, J., Benlabeled, M., Curzi, L., Escourrou, P., Gaultier. (1989). Administration of maternal pethidine, does it possibly induce secondary respiratory depression in the newborn with a normal Apgar score at birth? *Ann Fr Anesth Reanim*, 8-70.
- Hodgkinson, R., Bhatt, M., Grewal, G., Marx, G.F. (1978). Neonatal neurobehavior in the first 48 hours of life: effect of the administration of meperidine with and without naloxone in the mother. *Pediatrics*, 62(3), 294-8.
- Nissen, E., Lilja, G., Matthiesen, A.S., Arvidson, A.B., Moberg, K. (1995). Effects of maternal pethidine on infants developing breastfeeding behavior. *Acta Paediatrica*, 84, 140-145.

- Giannina, G., Guzman, E.R., Lai, Y.L., Lake, M.F. (1995). Comparison of the effects of meperidine and nalbuphine on intrapartum fetal heart rate tracings. *Obstetricians and Gynecologists*, 86(3), 1-3.
- Khooshideh, M. & Shahriari, A. (2009). A Comparison of Tramadol and Pethedine analgesia on the duration of labour: A Randomised Clinical Trial. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 49, 59-63.
- Konefał, H., Jaskot, B., Czeszyńska, M.B. (2012). Pethidine for labor analgesia; Monitoring of newborn heart rate, blood pressure and oxygen saturation during the first 24 hours after the delivery. *Ginekol Pol*, 83(5), 357-62.
- Yousefshahi, F., Asadi, M., Rahimi, F., Hoseinzade, M.J., Tanha, F.D., Barkhordari, K, et al. (2013). The effect of meperidine on peripartum breastfeeding and neonatal weight. *J Family Reprod Health*, 7(1), 29-34.
- Ullman, R., Smith, L.A., Burns, E., Mori, R., Dowswell, T. (2010). Parenteral opioids for maternal pain relief in labour. *Cochrane Database of Systematic Reviews*. Art. No.: CD007396.
- Comart, N. (2006). Elektronik Fetal Kalp Hızı Monitörizasyonu: Normal monitör, Fetal stres, Fetal distress İle İlişkili Erken Neonatal Sonuçlar. [dissertation]. Istanbul.
- Tsui, M.H.Y., Warwick, D., Kee, N., Floria, F., Lau, T.K. (2004). A double blinded randomised placebo-controlled study of intramuscular Pethedine for pain relief in the first stage of labour. *BJOG*, 111, 648-655.
- Fienni, S., Angeri, F., Kaihura, C.T., Ricci, L., Bedocchi, L., Galanti, B., et al. (2000). Evaluation of the peripartum effects of 2 analgesics: Meperidine and Tramadol, used in labor?. *Acta Biomed Ateneo Parmense*, 71(1), 397-400.
- Belfrage, P., Boreus, L.O., Hartvig, P., Irestedt, L., Raabe, N. (1981). Neonatal depression after obstetrical analgesia with Pethedine, the role of the injection- delivery time interval and of the plasma concentrations of Pethidine and Norpethidine. *Acta Obstet Gynecol Scand*, 81(1), 43-9.
- Reynolds, F., Sharma, S.K., Seed, P.T. (2002). Analgesia in labour and fetal acid-base balance: A meta analysis comparing epidural with systemic opioid analgesia. *BJOG*, 109, 1344-1353.
- Tuckey, J.P., Prout, R.E., Wee, M.Y.K. (2008). Prescribing intramuscular opioids for labour analgesia in consultant-led maternity units: A survey of UK practice. *International Journal of Obstetric Anesthesia*, 17(1), 3-8.