# High Copeptin Concentrations in Umbilical Cord Blood after Vaginal Delivery and Birth Acidosis

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**Context:** The pituitary-secreted nonapeptide arginine-vasopressin (AVP) is unstable and therefore unsuited for diagnostic use, but its secretion can be estimated by measuring copeptin, the C-terminal portion of the AVP precursor (pro-AVP).

**Objective:** Our objective was to investigate perinatal factors affecting copeptin concentrations in infants at birth and at 3 d of life.

**Design and Setting:** We conducted a prospective cross-sectional study at a tertiary university hospital.

**Patients:** Copeptin plasma concentrations were evaluated in 177 infants at birth, including 117 paired arterial/venous umbilical cord and 102 venous blood samples obtained at 3 d of life.

**Main Outcome Measure:** Copeptin concentrations were determined by a C-terminal pro-AVP luminescence immunoassay.

**Results:** Arterial umbilical cord copeptin concentrations were consistently higher than matched venous ones (median 18 *vs.* 10 pmol/liter, $P < 0.001$), but both values were closely related ($R_s = 0.825$; $P < 0.001$), and both were negatively related to arterial umbilical cord pH ($R_s$ arterial/venous $= -0.578/-0.639$; $P < 0.001$). Although exceedingly high copeptin concentrations were observed after vaginal birth in umbilical cord arterial [median (5–95% range) = 1610 (85–5000) pmol/liter] and venous [793 (6–4836) pmol/liter] plasma, copeptin concentrations were low after primary cesarean section [arterial/venous = 8 (3–907)/5 (5–504) pmol/liter]. Postnatal body weight loss was associated with increased copeptin concentrations at d 3 ($R_s = 0.438$; $P < 0.001$) and was inversely related to copeptin concentrations at birth ($R_s = -0.289$ and $-0.309$; both $P = 0.001$).

**Conclusion:** Vaginal birth is associated with a large release of copeptin that exceeds all values published so far, including those in critically ill adult patients with shock or brain injury. Thus, vaginal birth is arguably the most intense stressor in life. **(*J Clin Endocrinol Metab* 95: 5091–5096, 2010)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-1331 Received June 11, 2010. Accepted July 20, 2010.
First Published Online August 11, 2010

Abbreviation: AVP, Arginine vasopressin.

Crucial integration of a variety of neural and endocrine events is a prerequisite for the successful adaptation to extrauterine life. Parturition evokes a dramatic surge in stress hormones facilitating the transition of the newborn to air breathing, cardiovascular adaptation, thermogenesis, and glucose and water homeostasis.

The nonapeptide arginine-vasopressin (AVP), also known as antidiuretic hormone, is one of these stress hormones. AVP was first reported to be increased in cord blood more than 30 yr ago (1, 2). However, the measurement of AVP levels is laborious and for clinical use unsuited because of its instability and short half-life. AVP derives from a larger precursor peptide (provasopressin) together with two other peptides, neurophysin II and copeptin. Copeptin is released in an equimolar ratio to AVP, circulates in plasma without physiological activity, is highly stable especially after $Ca^{2+}$ chelation by EDTA, and easy to measure (3).

This study aimed to evaluate copeptin concentrations in paired samples of arterial and venous cord blood of newborn infants as well as in venous blood collected 3 d after birth.

## Subjects and Methods

The study was carried out between July and September 2009. After obtaining written informed consent, pregnant women presenting for delivery at the University Hospital Zurich, Switzerland, were included. The study was approved by the institutional review board.

Of the 177 infants studied, 141 (80%) were term (37–41 completed weeks of gestational age), 21 were near term (35 or 36 wk), and 15 had a gestational age of 32–34 wk. Twenty-four (13.6%) infants were twins, and three (1.7%) triplets. Sixty-two of the 177 infants were delivered vaginally (35%), including 17 (9.6%) requiring instrumental support; 115 (65%) were delivered by cesarean section, including 40 cases of secondary cesarean section due to acute fetal or maternal distress. The percentage of deliveries by cesarean section was significantly higher in preterm infants (31 of 36, 86%) than in term infants (83 of 141, 59%, $P = 0.003$).

Blood samples were drawn from 143 umbilical veins at the time of delivery with an additional 117 paired samples from umbilical artery and an additional 68 paired samples from venous blood at postnatal d 3. Auxiliary blood samples were taken at postnatal d 3 from 34 children.

Details of pregnancy (presence or absence of preeclampsia, diabetes, infection, preterm labor, or administration of betamethasone for fetal lung maturation), delivery (umbilical artery pH, base deficit, and hematocrit and amount of maternal blood loss), and the infants' birth characteristics (gestational age, birth weight, and Apgar scores at 5 and 10 min) were collected from the charts. The data on infants' health after birth, whether the infants were exclusively breastfed, additionally fed with formula, or given iv fluid, and the daily weight control were recorded by the staff on the maternity or neonatology ward, respectively. Characteristics of mothers and infants are summarized in Table 1.

Blood samples were collected immediately after birth by puncture of the umbilical cord artery and vein and at 72 h (±8 h, postnatal d 3) after birth by puncture of a vein from the back of the hand. After collecting blood in EDTA tubes, samples were stored at 4 C not exceeding 4 h until centrifugation was performed, and plasma was transferred in a new EDTA tube and subsequently frozen at −28 C. Measurement was done in a single batch with a research sandwich immunoluminometric assay (B · R · A · H · M · S C-terminal pro-AVP luminescence immunoassay; B · R · A · H · M · S AG, Hennigsdorf, Germany) as described elsewhere (3), except that the capture antibody was replaced by a murine monoclonal antibody directed to amino acids 137-144 (GRAGAL) of pro-AVP.

Statistical analyses were made using PASW version 18.0 (SPSS Inc., Chicago, IL) with strictly nonparametric tests (Spearman's rank order correlation, Mann-Whitney *U* test, Kruskal-Wallis, or Fisher's exact test).

**TABLE 1.** Selected characteristics of mothers and their infants

| Characteristics | Venous plasma, umbilical cord (n = 143) | Arterial plasma, umbilical cord (n = 117) | Venous plasma, d 3 (n = 102) |
|---|---|---|---|
| Infant sex | | | |
| Male | 78 (55) | 69 (59) | 60 (59) |
| Infant birth weight (g) | | | |
| <2000 | 11 (8) | 6 (5) | 8 (8) |
| 2000–3000 | 47 (32) | 38 (31) | 26 (26) |
| 3001–4000 | 77 (54) | 66 (56) | 61 (61) |
| >4000 | 8 (6) | 7 (6) | 7 (7) |
| Infant gestational age at birth (completed weeks) | | | |
| Preterm 32–37 | 32 (22) | 26 (22) | 20 (20) |
| Term 37–41 | 111 (78) | 91 (78) | 82 (80) |
| Mode of delivery | | | |
| Cesarean section primary | 74 (52) | 63 (54) | 42 (42) |
| Cesarean section secondary | 26 (18) | 23 (20) | 21 (21) |
| Spontaneous vaginal | 30 (21) | 23 (20) | 28 (28) |
| Instrumental vaginal | 13 (9) | 8 (7) | 11 (11) |

Results are shown as n (%).

## Results

Paired umbilical cord arterial and venous plasma copeptin concentrations were closely related (n = 117; $R_s = 0.825$; $P < 0.001$). Copeptin concentrations were consistently higher in arterial than in venous samples (median 18 *vs.* 10 pmol/liter, $P < 0.001$). Copeptin concentrations measured at 3 d of life [n = 102; M (5–95% range) = 14.0 (5.5–56.6) pmol/liter] were significantly ($P < 0.001$) lower than copeptin concentrations in either umbilical cord arterial or venous plasma. There was not a correlation of copeptin concentrations in paired samples of arterial umbilical cord plasma and d 3 venous plasma (n = 54; $R_s = -0.061$; $P = 0.664$) or in paired samples of venous umbilical cord plasma and d 3 venous plasma (n = 68; $R_s = -0.133$; $P = 0.281$).

Analyzing copeptin concentrations in respect to clinical dates revealed a significant ($P < 0.001$) inverse correlation of copeptin concentrations in both arterial umbilical cord plasma and venous umbilical cord plasma with umbilical artery pH ($R_s = -0.639$ and $-0.578$, respectively) and umbilical artery base excess ($R_s = -0.645$ and $-0.638$, respectively), as shown in Fig. 1. Apgar scores at 5 and 10 min of life and hematocrit in umbilical cord blood as well as mothers' blood loss during delivery did not correlate with copeptin concentrations in any plasma samples, neither arterial and venous umbilical cord plasma nor plasma samples drawn at d 3.

The mode of delivery affected copeptin concentrations in arterial and venous umbilical cord plasma very strongly (both $P < 0.001$) (see Fig. 1) but had no impact on copeptin concentrations in d 3 venous plasma. The distributions of copeptin concentrations in arterial and venous umbilical cord plasma with respect to the various delivery modes are summarized in Table 2.

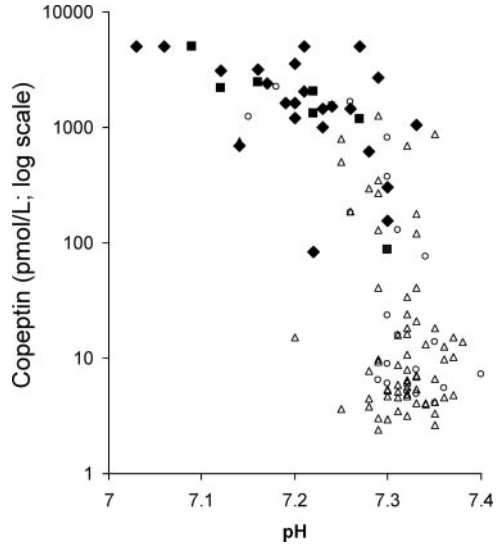


**FIG. 1.** Association of copeptin concentrations with pH in arterial umbilical cord samples. Data points are represented according to the delivery mode: ◆, vaginal spontaneous; ■, instrumental; △, cesarean primary; ○ cesarean secondary.

Gestational age was found to be directly related with copeptin concentrations in arterial and venous umbilical cord plasma ($R_s = 0.377$ and 0.416, respectively; both $P < 0.001$) but not with copeptin concentrations in d 3 venous plasma. However, birth weight depicted only a weak correlation to copeptin concentrations in venous umbilical cord plasma ($R_s = 0.183$; $P = 0.029$) but not with copeptin concentrations in either arterial umbilical cord plasma or d 3 venous plasma. This finding of lower copeptin concentrations in umbilical cord blood of infants born preterm or with low birth weight was mainly attributed to the fact that the percentage of deliveries by cesarean section was significantly higher in preterm infants (31 of 36, 86%) than in term infants (83 of 141, 59%, $P = 0.003$).

The maximal weight loss in postnatal adaptation occurred between d 2 and 5, on average at d 3. Intravenous fluid was administered in eight infants, all of whom weighed less than 1800 g at birth and therefore received iv fluid following institutional guidelines. Only 40 infants of the study population were exclusively breastfed, 62 received some additional hydrolyzed starch solution, and 67 received formula milk with or without mother's milk.

There was an inverse relation between maximal weight loss and copeptin concentrations in arterial as well as in venous umbilical cord plasma ($R_s = -0.309$ and $-0.289$, respectively; both $P = 0.001$), indicating increased postnatal weight loss in infants with low copeptin concentrations at birth. Then we compared copeptin concentrations in venous umbilical cord plasma in all infants subdivided in groups with mild (2–5%, n = 33), moderate (6–7%, n = 51), and severe maximal (8–12%, n = 53) postnatal weight loss. Copeptin concentrations at birth were significantly higher in infants with mild compared with moderate or severe maximal postnatal weight loss ($P = 0.017$ and $P < 0.0001$, respectively; Fig. 2A).

Maximal weight loss correlated directly with copeptin concentrations in venous plasma drawn at 3 d of life ($R_s = 0.438$; $P < 0.001$) but not with sodium concentrations, hematocrit, or bilirubin at d 3. All infants with copeptin values from d 3 were subdivided in groups with mild (n = 29), moderate (n = 36), and severe maximal (n = 37) postnatal weight loss. Copeptin concentrations at d 3 were significantly higher in infants belonging to the group with severe compared with mild or moderate maximal weight loss ($P < 0.0001$ and $P = 0.011$, respectively; Fig. 2B).

There was not a relation between maximal weight loss and gestational age at birth or between maximal weight loss and birth weight.

**TABLE 2.** Copeptin intervals in arterial and venous umbilical cord plasma

| Mode of delivery | n | Median copeptin (pmol/liter) | 95% reference interval (pmol/liter) | $P^a$ |
|---|---|---|---|---|
| Cesarean primary | 63/73 | 8/5 | 3–907/5–504 | |
| Cesarean secondary | 23/27 | 14/11 | 4–2240/2–2260 | <0.01/<0.01 |
| Vaginal spontaneous | 23/30 | 1610/634 | 82–5000/6–5000 | <0.001/<0.001 |
| Vaginal instrumental | 8/13 | 1786/1324 | 1786–5000/90–4900 | <0.001/<0.001 |

Results are shown as arterial/venous.

[a] Significance between cesarean primary and with each other mode of delivery.

## Discussion

Until now, copeptin had been studied exclusively in adults. These studies were done with respect to changes in plasma osmolality, in settings of mild to life-threatening physical stress, and in various diseases. Normal copeptin concentrations in healthy adults were consistently reported to be about 5 pmol/liter, as reviewed by Morgenthaler *et al.* (4). Water deprivation has been shown to increase copeptin concentrations 4-fold [M 19.9 (± SD 4.8) pmol/liter] (5), and severe stress, *e.g.* extubation of surgical patients, was found to result in a 10-fold increase [M 67.5 (interquartile range 37.8–110) pmol/liter] (6). The most pronounced surges in copeptin hitherto described were in patients suffering from shock, either septic [M 375 (range 59–1572) pmol/liter] (7) or hemorrhagic [M 269 (range 241–456) pmol/liter] (8). These 20-fold increased copeptin concentrations in adults suffering from life-threatening events are still far below the copeptin concentrations we measured in healthy, naturally delivered infants. Determination of copeptin concentrations in all these studies investigating adults was performed by the same C-terminal pro-AVP luminescence immunoassay as applied here, allowing for a direct comparison. Thus, vaginal delivery provokes a unique surge in copeptin plasma concentration (Fig. 1) incommensurable with all reported changes in copeptin concentrations in adult patients.

Hypoxia has been described to augment a strong AVP release within a short time in various animal models (9–13), and similarly, perinatal asphyxia in humans has been found to trigger a decisive AVP response (14, 15). Because also normal vaginal delivery in humans has been shown to trigger AVP release (1, 2), some investigators have come up with the hypothesis that fetal AVP release may effectively reduce placental blood flow during uterine contraction. This could contribute to acute fetal stress and hypoxia even during normal labor (16–18). However, our finding that copeptin concentrations in umbilical cord plasma are orders of magnitude (on average 500 times) higher in infants delivered vaginally compared with those delivered by elective cesarean section indicate that vaginal birth is the largest stressor for the body found so far, *e.g.* larger than brain trauma, ischemic stroke, or severe shock in adults (7, 8, 19, 20).

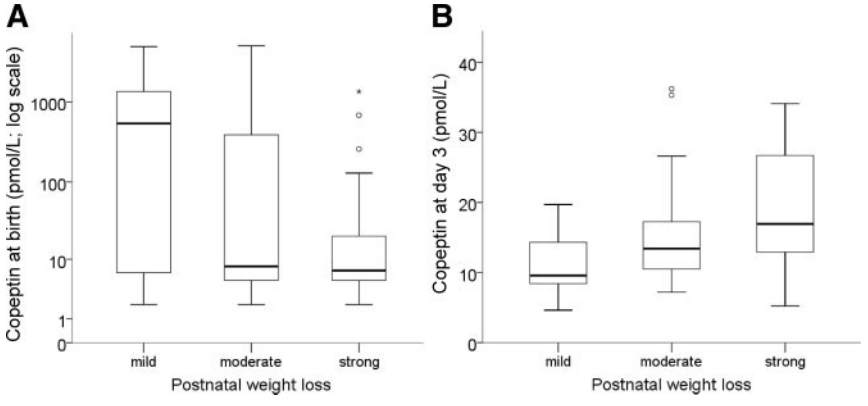


**FIG. 2.** A, Correlation of copeptin in venous umbilical cord plasma with maximal postnatal weight loss. Maximal postnatal weight loss is grouped in mild (2–5%, n = 33), moderate (6–7%, n = 51), and strong (8–12%, n = 53) loss. Data are presented as *box* (interquartile range) and *whisker* (5–95% range) plots. Significant statistical differences were noted between the following groups: mild *vs.* moderate ($P = 0.017$) and mild *vs.* strong ($P < 0.0001$). No significant difference was noted between moderate *vs.* strong ($P = 0.27$). B, Correlation of copeptin in venous plasma at d 3 with maximal postnatal weight loss. Maximal postnatal weight loss is grouped in mild (2–5%, n = 29), moderate (6–7%, n = 36), and strong (8–12%, n = 37) loss. Data are presented as *box* (interquartile range) and *whisker* (5–95% range) plots. Significant statistical differences were noted between the following groups: mild *vs.* moderate ($P = 0.011$) and mild *vs.* strong ($P < 0.0001$). No significant difference was noted between moderate *vs.* severe ($P = 0.054$).

Copeptin concentrations in arterial umbilical cord plasma were found to be on average 1.8-fold above those in paired venous umbilical cord plasma samples. Because copeptin appears to be too large (39-amino-acid glycopeptide) to cross the placental barrier, this observation leads to two hypotheses. First, measured copeptin levels in cord blood are of fetal origin, and second, some circulating copeptin is captured during the placental passage. Copeptin is thought to be without physiological function, and therefore, the placental clearance is somewhat surprising.

In our study, most newborns were born at term, but 36 (20%) were born between 32 and 36 completed weeks of gestation. Although there was a

significant positive and moderate correlation of copeptin levels in arterial and venous cord blood with gestational age, there was no consistent relationship with birth weight. A closer view on this finding reveals that the high percentage of cesarean sections within the group of preterm infants (86%) accounted for their overall low copeptin levels. After adjusting for vaginal delivery and secondary cesarean section, the difference between term and preterm infants disappeared. This is in line with previous findings investigating AVP (16, 21). One important limitation of our analysis is the small group of premature infants included, and there were no infants under 32 wk gestational age, which represent the most vulnerable group of patients in neonatal intensive care units.

AVP orchestrates a magnitude of actions covering well-understood mechanisms including water retention and maintenance of blood pressure but also recently discovered roles in social behavior (22). Thus, it is intriguing to assume that AVP is involved in postnatal physical and behavioral adaptation (*e.g.* bonding). Reports linking elevated AVP at birth with delayed voiding (23, 24) are in support of the inverse relation of high copeptin in umbilical cord blood and minor postnatal weight loss we found in this study (Fig. 2A). This may offer an explanation why infants born by cesarean section are prone to dehydration more frequently then infants delivered vaginally (25). Increased rates of breathing disorders after cesarean delivery are common (26, 27), and it is tempting to speculate that low AVP after cesarean delivery is involved in compromised postnatal pulmonary adaptation. In contrast to peripheral vasculature, AVP leads to vasodilatation of pulmonary vasculature under hypoxic conditions through AVP receptor-mediated endothelial release of NO (28, 29). In addition, type II pneumocytes express AVP receptors and have been shown to secrete surfactant when exposed to AVP (30, 31). Thus, physiological hypoxia during vaginal birth causing a robust AVP release may prepare infants for successful postnatal adaptation, whereas infants delivered by primary cesarean section (that is before the onset of labor) have no relevant AVP release and are thus less well prepared to resume respiratory oxygenation.

Even exceedingly high copeptin concentrations at birth returned to near-normal values at d 3 of life; there was no correlation between concentrations at both time points. This is in agreement with data from AVP analyses (16, 21, 32, 33) and from copeptin analyses in adults with acute myocardial infarction (34). Already 24 h after pain onset, copeptin concentrations normalized in the majority of patients. Moreover, the inverse correlation of copeptin concentrations at d 3 and dehydration as indicated by the infants' weight loss implicates an intact osmotic AVP regulation (Fig. 2B). Copeptin concentrations at d 3 were in about the same range as documented for adults during adaptation to dehydration (5). Thus, we conclude that after releasing AVP at birth, there are neither unusual low copeptin concentrations afterward nor a hampered osmotic AVP regulation.

Although an increased AVP secretion at the time of birth appears to be beneficial with respect to lung function and water retention, the magnitude of the surge after normal vaginal delivery is surprising. Several hypotheses may be invoked. First, newborns might require disproportionately high AVP concentrations because of low receptor expression or receptor affinity in target tissues. Second, AVP has a pivotal role in adaptation after birth, warranting the effort. Third, AVP is released in high concentrations for binding to AVP receptor-expressing neurons, pituitary gland cells involved in ACTH release, and for oxytocin receptor activation linked to bonding (22). There is indeed a fast-growing wealth of data uncovering evolutionary conserved function of vasopressin in modulating complex social behavior and cognition.

Recent data have revealed copeptin as a novel, independent prognostic marker in adult patients with ischemic stroke (20) and with severe injury after brain trauma in adults (19). In these settings, copeptin was shown to be superior to various markers such as protein S-100B and neuron-specific enolase in predicting severity level and outcome (20). Severe perinatal asphyxia damages brain in a manner similar to ischemic stroke resulting in hypoxic-ischemic encephalopathy, and neonatologists are looking for novel independent prognostic markers to guide clinical decision making with respect to applying therapeutic hypothermia and counseling parents. Further studies may explore whether extremely high copeptin concentrations at birth or kinetic changes of copeptin concentrations after birth may herald poor outcome.

## Acknowledgments

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S.W. was supported by a Swiss National Science Foundation Career Award for Medical Scientists (33CM30-124101). The study was funded by in-house grants of the Departments of Neonatology and Obstetrics of the University Hospital Zurich, Switzerland.

Disclosure Summary: N.G.M. and U.H. are employed by B · R · A · H · M · S, the manufacturer of the copeptin assay for which it owns patent rights (B · R · A · H · M · S C-terminal pro-AVP luminescence immunoassay; B · R · A · H · M · S AG, Hennigsdorf/Berlin, Germany). The present study was not financed by B · R · A · H · M · S AG. The remaining authors have nothing to declare.

## References


1. **Chard T, Hudson CN, Edwards CR, Boyd NR** 1971 Release of oxytocin and vasopressin by the human foetus during labour. Nature 234:352–354
2. **Polin RA, Husain MK, James LS, Frantz AG** 1977 High vasopressin concentrations in human umbilical cord blood: lack of correlation with stress. J Perinat Med 5:114–119
3. **Morgenthaler NG, Struck J, Alonso C, Bergmann A** 2006 Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem 52:112–119
4. **Morgenthaler NG, Struck J, Jochberger S, Dünser MW** 2008 Copeptin: clinical use of a new biomarker. Trends Endocrinol Metab 19: 43–49
5. **Szinnai G, Morgenthaler NG, Berneis K, Struck J, Müller B, Keller U, Christ-Crain M** 2007 Changes in plasma copeptin, the c-terminal portion of arginine vasopressin during water deprivation and excess in healthy subjects. J Clin Endocrinol Metab 92:3973–3978
6. **Katan M, Morgenthaler N, Widmer I, Puder JJ, König C, Müller B, Christ-Crain M** 2008 Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. Neuro Endocrinol Lett 29:341–346
7. **Struck J, Morgenthaler NG, Bergmann A** 2005 Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. Peptides 26:2500–2504
8. **Morgenthaler NG, Müller B, Struck J, Bergmann A, Redl H, Christ-Crain M** 2007 Copeptin, a stable peptide of the arginine vasopressin precursor, is elevated in hemorrhagic and septic shock. Shock 28: 219–226
9. **Anderson RJ, Pluss RG, Berns AS, Jackson JT, Arnold PE, Schrier RW, McDonald KE** 1978 Mechanism of effect of hypoxia on renal water excretion. J Clin Invest 62:769–777
10. **Robillard JE, Weitzman RE, Burmeister L, Smith Jr FG** 1981 Developmental aspects of the renal response to hypoxemia in the lamb fetus. Circ Res 48:128–138
11. **Rose Jr CE, Godine Jr RL, Rose KY, Anderson RJ, Carey RM** 1984 Role of arginine vasopressin and angiotensin II in cardiovascular responses to combined acute hypoxemia and hypercapnic acidosis in conscious dogs. J Clin Invest 74:321–331
12. **Leffler CW, Busija DW, Brooks DP, Crofton JT, Share L, Beasley DG, Fletcher AM** 1987 Vasopressin responses to asphyxia and hemorrhage in newborn pigs. Am J Physiol 252:R122–R126
13. **Raff H, Kane CW, Wood CE** 1991 Arginine vasopressin responses to hypoxia and hypercapnia in late-gestation fetal sheep. Am J Physiol 260:R1077–R1081
14. **Ruth V, Fyhrquist F, Clemons G, Raivio KO** 1988 Cord plasma vasopressin, erythropoietin, and hypoxanthine as indices of asphyxia at birth. Pediatr Res 24:490–494
15. **Speer ME, Gorman WA, Kaplan SL, Rudolph AJ** 1984 Elevation of plasma concentrations of arginine vasopressin following perinatal asphyxia. Acta Paediatr Scand 73:610–614
16. **Hadeed AJ, Leake RD, Weitzman RE, Fisher DA** 1979 Possible mechanisms of high blood levels of vasopressin during the neonatal period. J Pediatr 94:805–808
17. **Pohjavuori M, Raivio KO** 1985 The effects of acute and chronic perinatal stress on plasma vasopressin concentration and renin activity at birth. Biol Neonate 47:259–264
18. **Ramin SM, Porter JC, Gilstrap 3rd LC, Rosenfeld CR** 1991 Stress hormones and acid-base status of human fetuses at delivery. J Clin Endocrinol Metab 73:182–186
19. **Kleindienst A, Brabant G, Morgenthaler NG, Dixit KC, Parsch H, Buchfelder M** 2010 Following brain trauma, copeptin, a stable peptide derived from the AVP precusor, does not reflect osmoregulation but correlates with injury severity. Acta Neurochir Suppl 106:221–224
20. **Katan M, Fluri F, Morgenthaler NG, Schuetz P, Zweifel C, Bingisser R, Müller K, Meckel S, Gass A, Kappos L, Steck AJ, Engelter ST, Muller B, Christ-Crain M** 2009 Copeptin: a novel, independent prognostic marker in patients with ischemic stroke. Ann Neurol 66:799–808
21. **Rees L, Forsling ML, Brook CG** 1980 Vasopressin concentrations in the neonatal period. Clin Endocrinol (Oxf) 12:357–362
22. **Donaldson ZR, Young LJ** 2008 Oxytocin, vasopressin, and the neurogenetics of sociality. Science 322:900–904
23. **Vuohelainen T, Ojala R, Virtanen A, Laatta J, Mörsky P, Uotila J, Tammela O** 2007 Predictors of AVP and TSH levels and the timing of first voiding in the newborn. Pediatr Res 62:106–110
24. **Vuohelainen T, Ojala R, Virtanen A, Holm P, Tammela O** 2008 Predictors of delayed first voiding in newborn. Acta Paediatr 97: 904–908
25. **Konetzny G, Bucher HU, Arlettaz R** 2009 Prevention of hypernatraemic dehydration in breastfed newborn infants by daily weighing. Eur J Pediatr 168:815–818
26. **van den Berg A, van Elburg RM, van Geijn HP, Fetter WP** 2001 Neonatal respiratory morbidity following elective caesarean section in term infants. A 5-year retrospective study and a review of the literature. Eur J Obstet Gynecol Reprod Biol 98:9–13
27. **Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB** 2007 Elective caesarean section and respiratory morbidity in the term and near-term neonate. Acta Obstet Gynecol Scand 86:389–394
28. **Evora PR, Pearson PJ, Schaff HV** 1993 Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. Chest 103:1241–1245
29. **Tagawa T, Imaizumi T, Endo T, Shiramoto M, Hirooka Y, Ando S, Takeshita A** 1993 Vasodilatory effect of arginine vasopressin is mediated by nitric oxide in human forearm vessels. J Clin Invest 92: 1483–1490
30. **Walker BR, Haynes Jr J, Wang HL, Voelkel NF** 1989 Vasopressin-induced pulmonary vasodilation in rats. Am J Physiol 257:H415–422
31. **Brown LA, Chen M** 1990 Vasopressin signal transduction in rat type II pneumocytes. Am J Physiol 258:L301–L307
32. **Pohjavuori M, Fyhrquist F** 1980 Hemodynamic significance of vasopressin in the newborn infant. J Pediatr 97:462–465
33. **Leung AK, McArthur RG, McMillan DD, Ko D, Deacon JS, Parboosingh JT, Lederis KP** 1980 Circulating antidiuretic hormone during labour and in the newborn. Acta Paediatr Scand 69:505–510
34. **Khan SQ, Dhillon OS, O'Brien RJ, Struck J, Quinn PA, Morgenthaler NG, Squire IB, Davies JE, Bergmann A, Ng LL** 2007 C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) study. Circulation 115:2103–2110