Natural and Synthetic Oxytocin—Structurally Same but Differ in Effects—A Pilot Study

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Research Article

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Abstract

**Purpose:** synthetic oxytocin is currently used to induce labor and strengthen the contractile function in the first or second stage of labor. It is also used therapeutically and prophylactically in the third stage of labor. We aimed to correlate the dose and duration of synthetic oxytocin infusions used during induction of labor, augmentation of labor in the first and second stage of labor, and during active management of labor in the third stage of labor to the level of prolactin and cortisol in the serum of the parturient blood and from the umbilical cord vein.

**Methods:** The mother’s blood was collected from a venous vessel and foetal from the umbilical cord vein just cutting was performed and the levels of cortisol and prolactin was evaluated by electrochemiluminescence (ECLIA). The blood sample from the umbilical cord vein and artery were collected to separate heparinized capillaries and the pH, base deficit (BD), pO₂, and CO₂ concentration were assessed.

**Results:** We observed decreased level of prolactin immediately after the labor depending on the total dose of synthetic oxytocin used. We did not observe any relationship between the level of prolactin on postpartum day 2 on the dose of administered hormone or the fact of the labor induction. We observed significant correlations with regard to hormone levels without the synthetic oxytocin total dosage correlation.

**Conclusion:** We strongly believe that the definition of uniform norms and principles with regard to the dosage of synthetic oxytocin for labor induction should be determined.

Introduction

Oxytocin was first described to stimulate uterine muscle by Dale [1]. The term “oxytocin” is related to the Greek term “οξυκνεξ” and “τοκοκοξεξ,” meaning “quick delivery” [2]. It is synthesized, similar to vasopressin, by the large cellular neurons located in the neurons of the supraoptic and paraventricular hypothalamic nuclei, transported in combination with the neurophysins in axons in the form of neurogenic granules to the posterior pituitary lobe, and stored there. In the hypothalamus, it is present as an inactive precursor. The inactive precursor gradually hydrolyzes into smaller fragments and relocates along axons to the posterior pituitary lobe leading to its activation [3]. It is released by the stimulation of receptors located in the nipples, vagina, and cervix [4].

The concentration of oxytocin during pregnancy gradually increases, reaching its maximum during delivery and maintaining its high levels in the third and fourth stages of labor. Oxytocin is naturally secreted in the cerebrospinal fluid in high quantities, thereby directly affecting the female brain [5]. In this way, the stress level in the mother decreases, her mood improves, and specific behavioral patterns develop, which is closely related to the feeling of motherhood and the formation of an emotional bond with the newborn baby [5,6]. These effects are possible due to the presence of oxytocin receptors in the following structures of the brain: the dorsomedial hypothalamic nucleus, amygdala, septum pellucidum,
bed nucleus of the stria terminalis, anterior olfactory nucleus, preoptic and ventral tegmental area, and hippocampus [2]. Although oxytocin is secreted continuously in the central nervous system, it is released into the bloodstream by pulsation. The pulsating secretion depends on the depolarization of the cell membrane of the posterior pituitary lobe neurons, which occurs as a result of specific stimuli [2,5–8].

Synthetic oxytocin was first obtained in 1953 by Vincent du Vigneaud [2]. It is currently used as an integral part of clinical practice in obstetrics to increase the contraction of the uterine muscles—both to induce labor and strengthen the contractile function in the first or second stage of labor. It is also used therapeutically and prophylactically in the third stage of labor for accelerating the involution of the uterus and preventing postpartum bleeding [6–10]. The structure of synthetic oxytocin is identical to that of the natural hormone—it is a cyclic peptide containing nine amino acids. Increasing the permeability of the cell membrane to Ca\(^{2+}\) ions leads to a decrease in the membrane tension and an increase in excitability. This causes an increase in the amplitude, frequency, and duration of the contraction of uterine smooth muscle cells and nipple myoepithelial cells [2,5,6]. The oxytocin receptors, which belong to the group of protein G-binding receptors, are highly present in the limbic system, spinal cord, heart, intestine, immune system, uterus, and breast tissues [3,8].

According to some researchers, the key difference in the action of synthetic oxytocin is the fact that it does not penetrate the blood-brain barrier in the parturient. This is theoretically impossible due to the particle size and its hydrophilic nature [5–7,11], but according to some studies, intravenous or nasal administration allows oxytocin to penetrate into the intracerebral structures, which is beneficial to the selected patient groups [12–15]. However, this data does not apply to parturients.

In the context of childbirth, high-dose, continuous infusions of oxytocin usually result in regular uterine contraction, but the absence or average permeability of the blood-brain barrier and the continuity of infusions, unlike the pulsed release of natural oxytocin, may result in a different effect from the physiological hormone. The contractions are more painful according to the mothers giving birth, the concentration of stress hormones in the serum increases [12,13]

**Aim of the study**

In this study, we aimed to correlate the dose and duration of synthetic oxytocin infusions used during induction of labor, augmentation of labor in the first and second stage of labor, and during active management of labor in the third stage of labor to the level of prolactin and cortisol in the serum of the parturient blood during the course of full-term pregnancy: during admission to labor, during the third stage of labor (before the infusion with oxytocin is started), on the second day postpartum. To evaluate the newborn baby: prolactin and cortisol levels were measured and gasometry from the umbilical cord vein just cutting was performed.

**Material And Methods**
The study comprised of patients who were either admitted to the K. Marcinkowski Gynecological and Obstetrical Clinical Hospital in Poznan for the induction of labor and/or those in the active phase of the first stage of labor. This is a prospective cohort study. The inclusion criteria were as follows: single pregnancy, no contraindications to the natural labor at the time of qualification, gestational age between 37 and 42 weeks, and no fetal defects. A total of 81 patients gave their written informed consent to participate in the study. Patient enrollment methods, methods of obtaining the research material, and its storage were previously approved by the Poznan University of Medical Sciences Bioethics Committee, No. 869/19 (specifically approved only for this study on 12th September, 2019). The patients provided written informed consent for this study.

At this stage, after decontamination of the puncture site, blood was collected from a venous vessel using a closed aspiration and vacuum set SARSTEDT S-MONOVETTE 9 mL, containing a clotting activator (silicate). The sample collected was labeled with the date and time of collection, along with the term “Oxytocin 1” and was transferred to the laboratory, where the level of cortisol and prolactin was evaluated by electrochemiluminescence (ECLIA) using Cobas 6000 apparatus. Taking daily fluctuations in serum cortisol levels into account, the first sampling was performed in the morning. Before starting with the cortisol analysis, the hourly range, corresponding to the hours of sampling, was marked in relation to the cortisol test (6–10 and 16–20). In the case of high concentrations of hormone, reassessment was performed after sample dilution.

Seventy-eight patients provided the first blood sample. Of them, 66 women gave birth naturally, out of which, the blood sample was collected from 65 patients immediately after the birth in order to reassess the levels of prolactin and cortisol. This sample was labeled as “Oxytocin 2.” After the cessation of umbilical cord pulsation and after the sterile clamping and cutting, the blood sample was collected from the umbilical cord vein in a group of 61 women. This sample was labeled with the date and time of collection along with the terms “Umbilical cord oxytocin.” The blood sample was also collected from the umbilical cord vein and artery in order to separate heparinized capillaries and assess the pH, base deficit (BD), pO₂, and CO₂ concentration. The analysis was performed immediately after the blood collection using Cobas B 123 apparatus.

In the case of the remaining patients, 9 underwent labor with the use of a vacuum extractor and 6 underwent a Cesarean section. These patients were excluded from the subsequent stages of the study, which they were informed at the stage of qualification.

Out of 60 patients who gave birth naturally, we collected the blood sample from a venous vessel on postpartum day 2 in order to determine the levels of prolactin and cortisol. This sample was labeled “Oxytocin 3.”

The reasons for the loss of patients, apart from the fact that the birth was terminated during the surgical procedure, were as follows: sudden indications for Cesarean sections (no sampling “Oxytocin 1” – 3 patients), heavy postpartum bleeding after obtaining written consent (no sampling “Oxytocin 2” – 1
patient), insufficient blood in the umbilical cord vessels (no “Umbilical cord oxytocin” sampling, 5 patients), earlier discharge of the patient from our hospital (no sampling “Oxytocin 3” – 6 patients).

Ultimately, 59 patients with 1, 2, 3, and umbilical cord blood samplings were finalized (Scheme 1). We were able to collect umbilical cord blood samples from all patients to determine pH, BD, pO₂, and CO₂, but in some cases, it was not possible as there was insufficient blood in the umbilical cord vessels or due to rapid clotting of the sample, which made analysis impossible (Scheme 2).

**Results**

A total of 81 women agreed to participate in this study. The participants were recruited based on the following inclusion criteria: singleton pregnancy, not complicated by severe maternal or fetal disease, gestational age from 37+0 to 42+0 weeks, and no existing contraindications to natural labor at the time of the interview. The women were admitted to the hospital either for delivery (starting uterine contraction) and/or for the induction of the labor with synthetic oxytocin.

**Characteristics of the study group**

In this study, participants were in the age group of 21 to 41 years. Of the 66 participants whose labor was natural, 45 were multiparous (68%), and for the remaining 21 participants, it was the first labor (32%). Natural labor without an incision of the perineum took place in 24 women (30%); natural labor with an incision of the perineum took place in 42 parturients (52%); in 9 respondents (11%), it was necessary to complete the labor by a surgical procedure using a vacuum extractor, and in 6 (7%) patients, a Cesarean section was performed (Table 1). In the study group, 25 (38%) were female and 37 (56%) were male infants born. In 4 cases (6%), there was no data related to the child’s gender. Out of 66 participants, 14 (21%) participants had gestational diabetes (G1 and G2), 25 (38%) had hypothyroidism, and 18 (27%) had other diseases.

| Method of labor                  | Number (n) | Cumulated number | Percentage (%) |
|---------------------------------|------------|-----------------|----------------|
| Natural labor with perineum incision | 42         | 42              | 52             |
| Natural labor without perineum incision | 24         | 66              | 30             |
| Vacuum extractor                | 9          | 75              | 11             |
| Cesarean section                | 6          | 81              | 7              |

**Course of labor and postpartum period**

The duration of the first stage of labor varied greatly (range = 40 min to 17 h 30 min). The condition of newborns, evaluated according to the V. Apgar score, was good or medium. In their first minute of life, 56 newborns (90.3%) were given 10 points, 4 newborns (6.5%) were given 9 points, and 2 newborns (1.6%)
were given 8 and 6 points each. In their fifth minute of life, only one newborn child was given 9 points (1.6%), and the remaining 61 newborns were given 10 points (98.4%) (Table 2).

Table 2. The condition of newborns, evaluated according to the V. Apgar scale (0–10pt.)

|                        | 10 pt. | 9 pt. | 8 pt. | 6 pt. |
|------------------------|--------|-------|-------|-------|
| Score at the end of 1st min. of life | 90.3% (n=56) | 6.5% (n=4) | 1.6% (n=1) | 1.6% (n=1) |
| Score at the end of 5th min. of life | 98.4% (n=61) | 1.6% (n=1) | — | — |

The following analgesics, nalbuphine and paracetamol via intravenous infusions and nitrous-oxide via inhalation, were administered during the labor. None of the parturients received pethidine or epidural anesthesia. Individual patients also received “other” drugs (such as levothyroxinum natricum, ursodeoxycholic acid or insulin at different doses). After the analysis, the influence of individual analgesics and “other” drugs on the concentration of prolactin and cortisol collected during the first stage of labor, immediately after delivery, and from the umbilical cord blood and on day 2 after delivery was not found.

Among the group of patients who gave birth naturally, 14 patients (21%) had to undergo labor induction, 49 patients (74%) spontaneously developed systolic function, and there was no data available for 3 patients (5%) with regard to the necessity of labor induction.

In relation to systolic enhancement in the first stage of labor, oxytocin was administered to 7 parturients (11%), 55 women (83%) did not require oxytocin, and there was no data available for 4 patients (6%) in the first stage of labor are available.

In the second stage of labor, oxytocin was administered to 12 parturients (18%) to enhance contraction. Fifty women (76%) gave birth without additional stimulation, and there was no data available for 4 patients (6%) with regard to the enhancement of the systolic function in the second stage of labor.

The active management of labor by administering oxytocin after cutting of the umbilical cord was applied in 39 patients (59%); in 23 patients (35%), there was no infusion with oxytocin; and there was no data available for 4 patients (6%) with the regard to the active management of the third stage.

Among the 66 patients who gave birth naturally, the color of amniotic fluid was clear in 59 cases (89%), green in 3 cases (5%), and there was no data available for 4 cases (6%) with regard to the color of the amniotic fluid. Umbilical cord collision (umbilical cord wrapped around the neck, trunk, or limbs, or a true node on the umbilical cord) was found in 15 newborns (23%). In 4 cases (6%), there was no data with regard to the occurrence of umbilical cord collision, and there was no collision recorded for 47 children (71%).

During the first 2 h after the labor, 45 women (68%) breastfed the baby. For various reasons, 14 women (21%) were not able to breastfeed their baby, and there was no data was available for 7 women (11%).
Among the 78 women who provided their first blood sample, the minimum concentration of prolactin 1, collected before or during the first stage of labor, was 67.24 ng/mL and the maximum was 639.60 ng/mL. Of the 65 patients in whom blood was collected immediately after the labor, the lowest level of prolactin 2 was 40.75 ng/mL and the highest was 597.20 ng/mL. The level of prolactin determined from the umbilical cord vein (n=61) was between 125.90 nmol/L and 854.40 nmol/L. The concentration of prolactin 3 collected on day 2 after the labor (n=60) ranged from 187.80 nmol/L to 688.30 nmol/L.

**Statistical analysis of the results**

Our analysis shows that the level of prolactin 1, collected during the first stage of labor or before the infusion of synthetic oxytocin, was higher the older the woman was (p=0.049). A similar relationship was not observed in the case of sampling immediately after the labor and from the umbilical cord blood, as well as on day 2 after the labor.

A reduction in the levels of prolactin 2, in the sample collected immediately after the labor, depending on the total dosage of synthetic oxytocin used during the labor was also significant (p=0.019).

The higher the concentration of prolactin 1 before the labor, the lower was the level of cortisol 1 before the labor (p=0.000008) and the level of cortisol 2 immediately after the labor (p=0.012685). The higher the level of prolactin 1, the higher was the level of prolactin 2 immediately after the labor (p=0.002913) and prolactin 3, collected on day 2 postpartum (p=0.005651). We did not observe similar relationships with respect to the level of cortisol evaluated from the blood collected from the umbilical cord vein (p=0.062867), and cortisol 3 evaluated on day 2 after the labor (p=0.326436), as well as the concentration of prolactin collected from the umbilical cord vein (p=0.205800). The analysis of the relationship between prolactin 1 before the labor and gasometry values assessed immediately after the labor from the umbilical cord blood showed that an increase in prolactin 1 level is accompanied by a decrease in the pH and BD values (p=0.018081 and p=0.017754, respectively).

The level of cortisol 1 significantly correlated with the level of prolactin 1—the higher the values of cortisol 1, the lower was the concentration of prolactin (p=0.000008). An increase in the levels of cortisol 1 also positively correlated with an increase in the concentration of cortisol 2 (p=0.000000). Similarly, there was an increase in the levels of cortisol in the sample collected from the umbilical cord vein (p=0.000000) and serum levels on day 2 after the labor (p=0.001237). There were no significant correlations between the level of cortisol and prolactin 2 in the sample collected before the labor (p=0.262137) and between prolactin levels in the sample collected from the umbilical cord vein (p=0.276800) and prolactin on postpartum day 2 (p=0.428186).

Considering the relationship between the level of prolactin 2 immediately after the labor, we obtained a positive correlation between the level of prolactin 2 with prolactin 1 (p=0.002913), and prolactin 2 with the value of prolactin 3 on postpartum day 2 (p=0.000033). There was no correlation between the levels of prolactin 2 and cortisol 1 before the labor (p=0.262137), the levels of cortisol 2 immediately after the
labor (p=0.124322), the levels of prolactin and cortisol in umbilical cord blood (p=0.158318 and p=0.264867, respectively), and levels of cortisol on postpartum day 2 (p=0.946579).

Higher levels of cortisol 2 immediately after the labor correlated with lower levels of prolactin 1 and higher levels of cortisol 1 before the labor (p=0.012685 and p=0.000000, respectively). Higher levels of cortisol 2 positively correlated with the levels measured in umbilical cord blood and on postpartum day 2 (p=0.000000 and p=0.002897, respectively). There were no significant correlations between the level of cortisol 2 and prolactin 2 (p=0.124322) and between the levels of prolactin in umbilical cord blood (p=0.378587) and the level of prolactin on postpartum day 2 (p=0.329469).

With respect to the level of prolactin in umbilical cord blood, we did not obtain any significant relationships between the levels of prolactin 1 (p=0.205800), cortisol 1 (p=0.276800), prolactin 2 (p=0.158318), cortisol 2 (p=0.378587), and cortisol in umbilical cord blood (p=0.148877), and the levels of prolactin and cortisol on postpartum day 2 (p=0.513754 and p=0.301752, respectively).

The level of cortisol in the umbilical cord blood correlated strongly and positively with the level of cortisol 1 and cortisol 2 (p=0.000000 and p=0.000000, respectively). Apart from the above, there was no significant correlation between the level of prolactin 1 (p=0.062867), prolactin 2 (p=0.264867), and prolactin in the umbilical cord blood (p=0.148877), and the levels of prolactin and cortisol on postpartum day 2 (p=0.368646 and p=0.128370, respectively).

The level of prolactin 3 and prolactin 1, as well as prolactin 2, positively and significantly correlated (p=0.005651 and p=0.000033, respectively). However, there was no significant correlation between the value of prolactin 3 on postpartum day 2 and the values of cortisol 1 (p=0.428186), cortisol 2 (p=0.329469), prolactin and cortisol collected from umbilical cord blood (p=0.513754 and p=0.368646, respectively), as well as the level of cortisol 3 (p=0.690413).

The value of cortisol 3, on postpartum day 2 positively correlated with the value of cortisol 1 (p=0.001237) and cortisol 2 (p=0.002879). There was no significant correlation between the level of cortisol 3 and prolactin 1 (p=0.326436), prolactin 2 (p=0.946579), prolactin and cortisol determined in umbilical cord blood (p=0.301752 and p=0.128370, respectively), and the level of prolactin 3 on postpartum day 2 (p=0.690413).

The fact that a newborn baby first latched within 2 h after birth, which 45 women (68%) from the study group did (n of significant in this case =60), turned out to be important in the context of the concentration of the tested hormone and in relation to some of the obtained results. Among them, the level of prolactin 1 (p=0.009939) and lower levels of cortisol 1 during the first stage of the labor (p=0.010453), cortisol 2 immediately after the labor (p=0.010837), and from the umbilical cord blood (p=0.027262) were more frequently statistically significant.

At the end of pregnancy, the values of body mass index were not significantly related to the level of prolactin and cortisol during the first stage of labor, immediately after the labor, and from the umbilical
cord blood, as well as on postpartum day 2.

Table 3 and Figures 1–4 show a statistically significant relationship between the level of individual prolactin levels on the analyzed factors.

**Table 3. Statistically significant relationships between the level of individual prolactin measurements and the analyzed factors**
| Relationship                                                                 | No of significant (n) | Spearman's coefficient R | P-value       |
|------------------------------------------------------------------------------|-----------------------|--------------------------|---------------|
| Value of prolactin 1 and age of patients                                      | 65                    | 0.2449                   | 0.049192      |
| Value of prolactin 1 and cortisol 1                                          | 78                    | -0.482821                | 0.000008      |
| Value of prolactin 1 and cortisol 2                                          | 65                    | -0.307590                | 0.012685      |
| Value of prolactin 1 and 2                                                   | 65                    | 0.363549                 | 0.002913      |
| Value of prolactin 1 and 3                                                   | 60                    | 0.353108                 | 0.005651      |
| Value of prolactin 1 and pH - umbilical cord artery pH                       | 54                    | -0.320652                | 0.018081      |
| Value of prolactin 1 and BD - umbilical cord artery pH                       | 54                    | -0.321517                | 0.017754      |
| Value of cortisol 1 and prolactin 1                                           | 78                    | -0.482821                | 0.000008      |
| Value of cortisol 1 and cortisol 2                                            | 65                    | 0.718809                 | 0.000000      |
| Value of cortisol 1 and cortisol in umbilical cord blood                     | 59                    | 0.650614                 | 0.000000      |
| Value of cortisol 1 and cortisol 3                                            | 60                    | 0.407335                 | 0.001237      |
| Value of prolactin 2 and 1                                                   | 65                    | 0.363549                 | 0.002913      |
| Value of prolactin 2 and 3                                                   | 60                    | 0.508683                 | 0.000033      |
| Value of prolactin 2 depending on the total dose of synthetic oxytocin given | 56                    | -0.312441                | 0.019059      |
| Value of cortisol 2 and prolactin 1                                           | 65                    | -0.307590                | 0.012685      |
| Value of cortisol 2 and cortisol 1                                            | 65                    | 0.718809                 | 0.000000      |
| Value of cortisol 2 and cortisol in umbilical cord blood                     | 59                    | 0.834419                 | 0.000000      |
| Value of cortisol 2 and cortisol 3                                            | 60                    | 0.378088                 | 0.002897      |
| Value of cortisol in umbilical cord blood and cortisol 1                     | 59                    | 0.650614                 | 0.000000      |
| Value of cortisol in umbilical cord blood and cortisol 2                     | 59                    | 0.834419                 | 0.000000      |
| Value of prolactin 3 and 1                                                   | 60                    | 0.353108                 | 0.005651      |
| Value of prolactin 3 and 2                                                   | 60                    | 0.508683                 | 0.000033      |
| Value of cortisol 3 and 1                                                    | 60                    | 0.407335                 | 0.001237      |
| Value of cortisol 3 and 2                                                    | 60                    | 0.378088                 | 0.002897      |
| Relationship between the value of prolactin 1 and the fact of newborn        | 60                    | N/A                      | 0.009939      |
| Relationship between the value of cortisol 1 and the fact of newborn latching| 60                    | N/A                      | 0.010453      |
| Relationship between the value of cortisol 2 and the fact of newborn latching within 2 hours after the birth | 60 | N/A | 0.010837 |
| Relationship between the value of cortisol in umbilical cord blood and the fact of newborn latching within 2 hours after the birth | 60 | N/A | 0.027262 |

**Discussion**

According to the data obtained from the Childbirth with Dignity Foundation, collected in 2018, the percentage of induced labors in Poland during the study period was as high as 43% [16].

Based on the information collected from 12 countries, including Poland in 2020 [7], it is clear that the amount of the initial dose, the maximum dose, the time of increasing the flow of the infusion with oxytocin, as well as the sources of recommendations according to which in a given country the chosen procedure is adopted to induce labor through the use of the infusion with synthetic oxytocin are very divergent. Poland was among the countries where the guidelines concerning the analyzed parameters were regulated by institutions—hospitals where the infusion with synthetic oxytocin is turned on. The dose of oxytocin added to 50 mL of the solvent (0.9% saline or 5% glucose solution) in Poland was 5 IU, the initial dose ranged from 0.06 to 1.2 IU/h, the flow was increased every 30 min by 1.2 mL/h until 3 contractions lasting about 60 seconds within 10 min, the maximum flow was 18 mL/h [7]. It was similar in our study group of patients—1 mL of oxytocin preparation containing 5 IU/mL of solution was added to 49 mL of 0.9% saline or 5% glucose solution. The initial flow rate in all patients was 3 mL/h, which corresponds to a dose of 0.3 IU/h. Most often, the maximum dose needed to achieve satisfactory contraction was 6 mL/h; in a single case, it was 8 mL/h, and in another case, it was 10 mL/h. The frequency of contractions and fetal heart rate were monitored continuously. The total dose of oxytocin, administered during 8 h, was determined between 7.65 and 8.10 IU, whereas data from Germany indicate the administration of up to 27 IU of synthetic oxytocin during 8 h of labor induction. In Germany, the manufacturers provide instructions on doses as part of the hospital guidelines [7]. The total dose of synthetic oxytocin we evaluated was related to the duration of the entire labor, which was as follows: 5 IU—43 patients, 10 IU—13 parturients, and 20 IU—1 patient with uterine atony and postpartum hemorrhage. Interestingly, in the case of the patient with uterine atony, the total duration of the infusion was 9 h, and the maximum flow was 10 mL/h. It was necessary to turn on an additional 5 IU of oxytocin (in 500 mL of 5% glucose solution) in order to strengthen the contraction during the second stage of the labor. It was her second induction of labor. The first 10-hour induction attempt was made the day before the labor, also with the use of synthetic oxytocin, obtaining a maximum flow of 6.5 mL/h, but without the effect of regular uterine contraction.

This information may be extremely important. It may lead to the definition of uniform norms and principles with regard to the dosage of synthetic oxytocin for labor induction [17–19]. It is also important
in the context of the effect of the synthetic hormone on the reduction of the natural secretion of oxytocin in response to the “skin-to-skin” contact between the mother and the newborn [20]. According to a previous study on the influence of drugs that may affect the newborn taking of breast sucking during the first hour after the labor, it was demonstrated that the probability of the newborn baby taking breast sucking during the first 60 min after delivery decreases with an increase in the total dosage of synthetic oxytocin administered to the mother during the labor [9,21–24]. In the case of the group of patients we examined, we did not observe such a relationship. However, we observed significant correlations with regard to hormone levels. Mothers with higher levels of prolactin and lower levels of cortisol before the labor were more likely to breastfeed the newborn within 2 h after the labor. Among these women, the concentration of cortisol collected from the umbilical cord blood and immediately after the labor was also lower. These relationships seem to be interesting and worth further observation.

Jonas et al. [20] observed a significantly higher level of prolactin on postpartum day 2 in the group of women who received an infusion of synthetic oxytocin during the labor, with a simultaneous decrease in the level of endogenous oxytocin, especially in women who received epidural analgesia during the labor. This is a very interesting observation, because in our study group, there was a marked decrease in the level of prolactin immediately after the labor depending on the total dose of synthetic oxytocin used (p=0.019). We did not observe any relationship between the level of prolactin on postpartum day 2 on the dose of administered hormone or the fact of labor induction. However, it should be emphasized that none of the patients we examined had an epidural during the labor.

The condition of newborns assessed according to the V. Apgar scale at the end of their first minute of life was good or average and in the fifth minute of life, the condition of all the newborns was good. Similar results have been reported by Karaçor et al. [17], regardless of the fact of synthetic oxytocin administration. Similarly, the parameters of pH, BD, PO₂, and CO₂ were within the range of standards; however, due to the size of the study group in the pilot study, a wider evaluation is planned.

**Declarations**

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**Conflicts of interest/Competing interests:** The authors report no conflicts of interest.

**Availability of data and material:** data are available for you if needed.

**Code availability:** Not applicable.

**Ethics approval:** Patient enrollment methods, methods of obtaining the research material, and its storage were previously approved by the Poznan University of Medical Sciences Bioethics Committee, No. 869/19 (specifically approved only for this study on 12th September, 2019). The patients provided written informed consent for this study.
Consent to participate: The patients provided written informed consent for this study.

Consent for publication (include appropriate statements).

References

1. Dale HH. The action of extracts of the pituitary body. Bio-Chemical Journal, 1909:427–447
2. Viero C, Shibuya I, Kitamura N, Verkrhatsky A, Fujihara H, Katoh A, Ueta Y, Zingg HH, Chvatal A, Sykova E, Dayanithi G (2010) Oxytocin: Crossing the Bridge between Basic Science and Pharmacotherapy. CNS Neurosci Ther 16:138–156
3. Szukiewicz D, Bilska A, Mittal TK, Stangret A, Wejman J, Szewczyk G, Pyzlak M, Zamlynski J (2015) Myometrial contractility influences oxytocin receptor (OXTR) expression in term trophoblast cells obtained from the maternal surface of the human placenta. BMC Pregnancy Childbirth 15:220
4. Leng G, Pineda R, Sabatier N, Ludwig M (2015) 60 YEARS OF NEUROENDOCRINOLOGY: The posterior pituitary, from Geoffrey Harris to our present understanding. J Endocrinol 226(2):173–185
5. Uvnäs-Moberg K, Ekström-Bergström A, Berg M, Buckley S, Pajalic Z, Hadjigeorgiou E, Kotłowska A, Lengler L, Kielbratowska B, Leon-Larios F, Magistretti CM, Downe S, Lindström B, Dencker A (2019) Maternal plasma levels of oxytocin during physiological childbirth – a systematic review with implications for uterine contractions and central actions of oxytocin. BMC Pregnancy Childbirth 19:285
6. Bell AF, Erickson EN, Carter S (2014) Beyond labor: the role of natural and synthetic oxytocin in the transition to motherhood. J Midwifery Womens Health 59(1):35–42. doi:10.1111/jmwh.12101
7. Daly D, Minnie KCS, Bliignaut A, Blix E, Nilsen ABV, Dencker A, Beeckman K, Gross MM, Pehlke-Milde J, Grylka-Baeschin S, Koenig-Bachmann M, Clausen JA, Hadjigeorgiou E, Morano S, Iannuzzi L, Branowska B, Kiersnowska I, Uvnäs-Moberg K. How much synthetic oxytocin is infused during labour? A review and analysis of regimens used in 12 countries. PLoS ONE 2020;15(7):e0227941. https://doi.org/10.1371/journal.pone.0227941
8. Cadwell K, Brimdyr K (2017) Intrapartum Administration of Synthetic Oxytocin and Downstream Effects on Breastfeeding: Elucidating Physiologic Pathways. Annals of Nursing Research Practice 2(3):1024
9. Gabriel MAM, Olza Fernandez I, Martinez AMM, Armengod CG, Costarelli V, Santos IM, Fernandez-Canadas Morillo A, Perez Riveiro P, Lopez Sanchez F (2015) Garcia Murillo L. Intrapartum Synthetic Oxytocin Reduce the Expression of Primitive Reflexes Associated with Breastfeeding. Breastfeeding Medicine 10,(4):209–213
10. García-Fontea P, González-Mesa E, Blasco M, Cazorla O, Delgado-Ríos M, González-Valenzuela MJ (2014) Oxytocin administered during labor and breast-feeding: a retrospective cohort study. The Journal of Maternal-Fetal Neonatal Medicine 27(15):1598–1603. DOI:10.3109/14767058.2013.871255
11. Leng G (2000) Oxytocin. In: Fink G (ed) Encyclopedia of stress. Academic Press, San Diego, pp 109–114
12. Hollander E, Novotny S, Hanratty M et al (2003) Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger’s disorders. Neuropsychopharmacology 28:193–198
13. Shamay-Tsoory S, Fischer M, Dvash J, Harari H, Perach-Bloom N, Levkovitz Y (2009) Intranasal administration of oxytocin increases envy and schadenfreude (gloating). Biol Psychiatry 66:864–870
14. Guastella A, Howard A, Dadds M, Mitchell P, Carson D (2009) A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. Psychoneuroendocrinology 34:917–923
15. Muscatelli F, Desarmenien MG, Matarazzo V, Grinevich V (2018) Oxytocin Signaling in the Early Life of Mammals: Link to Neurodevelopmental Disorders Associated with ASD. Curr Topics Behav Neurosci 35:239–268
16. https://gdzierodzic.info/bazawiedzy/indukcja-porodu/. Dostęp 21.12.2020
17. Karaçor T, Sak S, Başaranoğlu S, Peker N, Ağaçayak E, Sak ME, Turgut A, Evsen MS, Evliyaoğlu O, Gül T (2017) Assessment of oxidative stress markers in cord blood of newborns to patients with oxytocin-induced labor. J Obstet Gynaecol 43,(5):860–865
18. Lefevre A, Sirigu A (2016) The two fold role of oxytocin in social developmental disorders: A cause and a remedy? Neurosci Biobehav Rev 63:168–176
19. Gu V, Feeley N, Gold I, Hayton B, Robins S, Mackinnon A, Samuel S, Carter CS, Zelkowitz P (2016) Intrapartum Synthetic Oxytocin and Its Effects on Maternal Well-Being at 2 Months Postpartum. Birth 43(1):28–35
20. Jonas W, Johansson LM, Nissen E, Ejdebäck M, Ransjö-Arvidsson AB, Uvnäs-Moberg K (2009 Jun) Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day postpartum. Breastfeed Med 4(2):71–82
21. Fernández IO, Gabriel MM, Martínez AM, Fernández-Cañadas Morillo A, Sánchez FL, Costarelli V (2012) Newborn feeding behaviour depressed by intrapartum oxytocin: a pilot study. Foundation Acta Pædiatrica 101:749–754
22. Velandia M. Parent-infant skin-to-skin contact studies: Parent-infant interaction and oxytocin levels during skin-to-skin contact after Cesarean section and mother-infant skin-to-skin contact as treatment for breastfeeding problems. Doctoral thesis. Karolinska Institute, Dept of Women's and Children's Health; 2012, Stockholm, Sweden. https://openarchive.ki.se/xmlui/bitstream/handle/10616/40879/Thesis_Marianne_Velandia.pdf?sequence = 1&isAllowed = y
23. Brimdyr K, Cadwell K, Widström A-M, Svensson K, Neumann M, Hart EA et al (2015) The Association Between Common Labor Drugs and Suckling When Skin-to-Skin During the First Hour After Birth. Birth Berkeley Calif 42:319–328
24. Bell AF, White-Traut R, Rankin K (2013) Fetal exposure to synthetic oxytocin and the relationship with prefeeding cues within one hour postbirth. Early Hum Dev 89(3):137–143

**Figures**

![Figure 1](image)

**Figure 1**

Relationship between the concentration of prolactin 1 and the fact of newborn latching within 2 hours after the birth.
Figure 2

Relationship between the concentration of cortisol 1 and the fact of newborn latching within 2 hours after the birth.
Figure 3

Relationship between the concentration of cortisol 2 and the fact of newborn latching within 2 hours after the birth.
Figure 4

Relationship between the concentration of cortisol determined from umbilical cord blood and the fact of newborn latching within 2 hours after the birth.

Supplementary Files

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- s1.png
- s2.png