Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Investigating the Relationship between Salivary Estriol to Progesterone Ratio and Onset of Labor: A Feasibility Study

Caroline Given
University of California, Irvine
Maren Smith
University of California, Irvine
Claudia Alvarez
Desert Regional Medical Center
Elena Rhoads
University of California, Irvine
Afshan Hameed
University of California, Irvine
Ninh Nguyen
University of California, Irvine
Robert Bristow
University of California, Irvine
Lourdes Swentek
lyrobles@hs.uci.edu
University of California, Irvine

Research Article

Keywords: Obstetrics and/or gynecology, endocrinology, salivary immunoassay

Posted Date: March 8th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8812856/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background: Salivary hormone levels of estriol (E3) and progesterone (P) have been studied as potential biomarkers for preterm and labor. Prior studies have reported a rise in the E3 to P ratio (E3:P) in the weeks leading up to spontaneous labor as well as an association between elevated E3 and preterm labor. This study sought to clarify if there was a daily rise in E3:P in term labor that could be captured in salivary samples and potentially indicate the onset of labor.

Methods: This was a single-center prospective pilot study aimed at evaluating E3:P in term pregnant females from 38 weeks until day of delivery. Secondary outcomes included E3, P, and E3:P variability and labor outcomes (spontaneous vaginal delivery, cesarean section, or induction). Participants self-collected daily salivary samples starting at 38 weeks gestational age leading up to delivery. A Wilcoxon signed-rank test was used to evaluate E3:P, estriol, and progesterone change prior to delivery. A Mann-Whitney U was utilized to compare median E3:P, estriol, and progesterone between the induced and spontaneous groups.

Results: We found no significant change in E3:P prior to labor onset ($p=0.81$) We also did not find a significant rise in estriol or progesterone alone prior to labor onset between subjects ($p=0.58$ and $p=0.23$). E3:P and estriol were significantly lower in those that were induced versus those who went into spontaneous labor ($p<0.001$ and $P<0.001$).

Conclusions: Although this study had limited power, higher E3:P ratios were significantly associated with spontaneous labor compared to induced labor, suggesting E3:P may serve as a clinical decision making tool for induction planning in term pregnancy.

BACKGROUND

Determining when a pregnant patient will begin labor remains a clinical challenge. Furthermore, determining whether labor has begun requires a pelvic exam. Clinicians lack a definitive, noninvasive method to determine when labor has truly begun before membrane rupture. This uncertainty forces pregnant patients to seek in-person assessment at labor and delivery triage units.[1] There, clinicians employ a combination of methodologies to assess the onset of labor and monitor the progression from the latent to active phase. These assessments include the evaluation of cervical dilation, cervical effacement, fetal station, and the observation of maternal symptoms.[1–3] Many pregnant people will experience Braxton Hicks contractions, also described as “false contractions” or practice contractions, during the course of their pregnancy, and upwards of 50% of patients presenting to labor and delivery triage patients are there to rule out labor.[4] These visits are costly, demand resources, and potentially carry an increased likelihood of intervention.[5–7] Given the complexity of predicting the onset of labor and differentiating between latent and active labor, biomarkers of parturition remain of interest to researchers. Although the mechanisms that trigger labor are likely complex and diverse, salivary

hormones remain appealing because samples are relatively inexpensive, transportable, and may be self-collected by participants at home.[8]

In a 1987 pilot study, Darne et al. used salivary samples to characterize the trends in estriol, estrogen, estradiol, and progesterone in the second and third trimesters of pregnancy, reporting that the ratio of estriol to progesterone (E3:P) rose from < 1 to > 1 in the last 5 weeks of pregnancy in all subjects.[9] Additionally, they described an acute rise in E3:P reporting that the median E3:P ratio rose acutely to > 1.65 24 hours prior to the onset of labor. Estriol is of little significance in a non-pregnant subject but has long been postulated to play a significant role in later stages of parturition.[10] It is hypothesized that dehydroepiandrosterone sulfate (DHEAS) is secreted by the fetal adrenal gland, converted to estriol in the placenta, and subsequently diffuses into maternal circulation, whereby it has consequences for myometrial activity by up-regulating synthesis of oxytocin receptors, prostaglandins, and formation of myometrial gap junctions.[10, 11] Estriol has therefore remained of interest as a potential predictor for preterm labor, which remains a leading cause of infant mortality in the United States and globally.[12] A masked, multicenter trial carried out by Heine et al. collected weekly salivary estriol samples from pregnant patients starting at 22 weeks demonstrated that salivary estriol testing outperformed Creasy scoring for predicting the onset of preterm labor.[13] Other studies have similarly reported associations between elevated E3:P in patients delivering before 34 weeks or, conversely, a lack of rise in estriol being associated with labor induction.[14,15] However, published literature has focused primarily on preterm labor and deliveries and there has been no further exploration of the acute rise in estriol or E3:P leading up to term labor onset reported by Darne et al..

The purpose of this project is to closely explore the salivary estriol to progesterone ratio in the days leading up to term delivery by applying similar principles from the existing literature and better establish if there is an acute change, potentially specific and quantifiable to individual pregnancies, that may be captured in the days leading up to term delivery. Specifically, we analyzed E3:P to best contextualize our study in comparison to previous studies. We hypothesize that there will be an acute change in the salivary E3:P in the 24-hour period before a participant presents to the hospital for delivery. We expect E3:P may vary greatly between subjects; however, we predict that daily changes leading up to delivery, irrespective of baseline E3:P at study onset, will trend consistently amongst subjects even if whole value saliva hormone levels differ. We hope to uncover evidence that there is potentially a measurable and reliable relationship between these ratios and labor onset, which would warrant further investigation with a larger study.

METHODS

This was a single-center prospective pilot study aimed at evaluating E3:P in term pregnant females from 38 weeks until day of delivery. Secondary outcomes included E3, P, and E3:P variability and labor outcomes. We received Institutional Review Board approval for the study. We screened and recruited potential subjects at their 36-week OBGYN appointment for inclusion and exclusion criteria. Inclusion

criteria were pregnant adults over 18 years of age who planned to deliver at the University of California Irvine (UC Irvine). Exclusion criteria were history of preterm labor, which was defined as delivering a baby before 37 weeks' gestation; pregnancy with twins, triplets, or other multiples; less than 18 months between conception of current pregnancy and previous childbirth; current use of tobacco or marijuana products; current or recent diagnosis (within 18 months) of substance use disorder; currently taking corticosteroid medications by mouth, topically, or by injection; and scheduled cesarean section or scheduled delivery via induction at time of enrollment. Exclusion criteria were established by author consensus and review of the literature to minimize risk for cesarean delivery as well as mitigate environmental factors that impact salivary hormone testing.[16, 17]

After informed consent, participants received in-person instructions, sample collection kits, and written instructions. Sample collection kits were distributed with access to online instructions at participant's OBGYN appointment with instruction to begin collection at 38 weeks (calculated using the American College of Obstetricians and Gynecologists' dating criteria).[18] We instructed participants to collect samples via passive drool at roughly the same time every day. Participants received a daily survey via email or text. The survey included questions relating to new onset labor symptoms and salivary sample collection conditions (Fig. 1). These included date and time of collection; if the participant had consumed food, drink, coffee, alcohol, or dairy prior to collection; any exercise prior to collection; if the participant had brushed or flossed teeth within an hour of collection; new medications started within the last 24 hours; and the time that the participant went to sleep and woke up. After sample collection, participants were instructed to place their samples in a freezer at or below 0° Fahrenheit (ask.usda.gov). Samples were then collected by the study team at the patient's home anytime between one to six weeks postpartum.

Samples were sent to UC Irvine's Institute for Interdisciplinary Salivary Bioscience for processing. ELISA was performed in duplicate to quantify estriol and progesterone in each salivary sample. Briefly, monoclonal antibodies to estriol were coated on 96-well plates and incubated for 2 hours with estriol conjugated to estriol linked horseradish peroxidase (HRP). A tetramethylbenzidine substrate was added and the reactions were stopped after 30 minutes with 2M Sulfuric Acid. Absorbance was measured at 450nm with a 490nm correction filter. Concentrations of controls and samples were calculated from a standard curve generated using a 4-parameter non-linear regression curve fit (Gen5, BioTek). Manufacturer-provided high and low controls fell within confidence limits. The same process was performed to quantify progesterone in salivary samples using progesterone-linked HRP.

All information was stored by UC Irvine's Institute for Interdisciplinary Salivary Bioscience and was then de-identified and stored in REDCap.

A Wilcoxon signed-rank test was used to evaluate E3:P, estriol, and progesterone change prior to delivery. A Mann-Whitney U was utilized to compare median E3:P, estriol, and progesterone between the induced and spontaneous groups. A Levene's test was used to compare variability between normalized E3:P, estriol, and progesterone datasets.

RESULTS

Salivary samples were successfully collected, documented, and analyzed for 8 pregnant patients at UC Irvine. The average number of samples per subject was 11 with a range of 5–17 samples provided. The average age of the participants was 33.5 years (range 28–41 years old). Six participants identified as white, one identified as Asian, and one declined to respond. Medical conditions of the cohort included asthma, hypothyroidism, hyperthyroidism, depression, anxiety, migraines, and seizure disorder. The average gestational age at labor onset was 39w4d with a range of 38w5d-40w5d. Three patients underwent induction for fetal bradycardia, non-reassuring fetal heart tracing, and vacuum-assisted induction, respectively. The other five patients underwent normal spontaneous vaginal deliveries. Of the 26 enrolled, 8 completed the study (30.1%). Of those who did not complete the study, 8 stopped self-collecting samples due to scheduled c-sections or inductions, 5 did not respond to schedule sample pickups, 3 withdrew, 1 collected samples without completing survey data, and 1 stopped attending her UC Irvine OBGYN appointments.

Daily E3:P samples of the 8 patients leading up to delivery are shown in Fig. 2. We found no significant rise of E3:P before delivery ($p = 0.81$). This was true between subjects, for example comparing E3:P in subjects A and B, and also observed in subjects' individual trends, which are provided in figures S1-S8.

As expected, there were large variations in E3:P, estriol, and progesterone between different pregnant participants. However, when the data was normalized and estriol, progesterone, and E3:P were compared using a Levene's test, they did not demonstrate significantly greater variability ($p = 0.81$) (Fig. 3). Raw salivary estriol levels in the participants ranged from 659–6438 pg/mL with a mean value of 2676.54 and a median of 2496 (Fig. 4). Similarly, raw progesterone levels ranged from 774–7075 pg/mL with a mean of 2832.48 and a median of 2277.5 (Fig. 5). E3:P ranged from 0.32–2.51 with a mean value of 1.07 and a median of 0.99 (Fig. 2).

Additionally, we found that overall E3:P was significantly lower in those that were induced versus those who went into spontaneous labor ($p < 0.001$) (Fig. 6). Similarly, amongst the patients who were induced, their estriol was significantly lower than those who went into spontaneous labor ($p < 0.001$) (Fig. 7). However, when comparing progesterone values between the induced and spontaneous labor groups, there was no significant difference ($p = 0.30$) (Fig. 8).

DISCUSSION

Our study failed to demonstrate a significant, acute rise in E3:P ratio prior to labor onset in term pregnancies. This was inconsistent with the study published by Darne et al., which examined 20 pregnant subjects and demonstrated an increase in salivary E3:P from < 1 to > 1 in every subject prior to delivery as well as an increase in median E3:P in the 24 hours prior to delivery.[9] Our findings also contradict those of Smith et al. who found a significant increase in serum E3 at labor onset and a significant decrease in P:E3 translating to an observed significant increase in E3:P in 58 singleton term

spontaneous deliveries.[19]However, this study compared serum values taken within 24 hours of delivery with an interpolated value of 4 weeks prior. We also did not see a significant rise in estriol prior to delivery or any significant changes in progesterone. While we postulated that baseline values of salivary hormones would differ greatly between participants, we anticipated they would trend consistently, but this was not apparent in our small sample. Our results were more consistent with the 2009 study by Lachelin et al. that collected weekly estriol and progesterone samples in 92 participants from 24 weeks gestation until delivery.[15] Samples were analyzed in subgroups of those who delivered prior to 34 weeks, those who delivered between 34 and 37 weeks, and those who delivered after 37 weeks. While results demonstrated that E3:P was significantly higher in the < 34 week group compared to the 34–37 week group and > 37 week group and that progesterone was significantly lower in the < 34 week group compared to the 34–37 and > 37 week group, they did not find any significant differences in progesterone, E3:P, and estriol when comparing the 34–37 and > 37 week groups. This implies that changes in estriol, though present throughout pregnancy, might have more significance for clinical implications earlier in gestation and may remain fairly stable later on. Additionally, this study suggests that the higher E3:P values seen in the < 34-week group is driven by low progesterone rather than high E3.

While we did not see an acute rise, we did find a significant correlation between a lower E3:P ratio and lower estriol in the participants requiring induction compared to those who went into spontaneous labor. We did not observe a significant difference in progesterone between the induced and spontaneous groups ($p = 0.30$), indicating that the observed difference in E3:P is due to low E3 rather than high P. Elevated estriol has been associated with preterm labor and deliveries in multiple studies. A study by McGregor et al. including 241 participants collected weekly samples starting at 22.5–26.5 weeks gestational age and found that a single estriol value > 2.3ng/mL predicted preterm labor or preterm delivery with 71% sensitivity and 77% specificity, also noting that elevated estriol more accurately identified patients in their study at risk for preterm labor and delivery than clinical risk factors or assessment.[20] A similar study by Heine et al. including 601 subjects, similarly found that a single estriol value of > 2.1ng/mL had a sensitivity and specificity of 64% and 68% for predicting preterm labor or delivery for high-risk patients included in their study (152 out of 601 patients).[21] Indeed, estriol is an FDA approved test for assessing risk for preterm labor. However, as demonstrated by other metrics reported in the Heine et al. study, it is not widely used in clinical practice due to its sensitivity and specificity profile.

Conversely, low estriol or low E3:P have not been rigorously evaluated in the literature as risk factors for post-term pregnancy or their utility in assessing the need for an induction of labor. A small study by Moran et al., describes a lack of rise in E3:P in patients requiring induction; however, this association is otherwise relatively absent in the literature.[14] This is likely because preterm labor and preterm delivery are far more pressing public health issues while inductions of labor are common and safe. The association between decreased E3:P and estriol demonstrated in our study is consistent with those published in a smaller study by Hedriana et al. that analyzed weekly samples from 16 participants from

30 weeks to delivery.[22] Results were grouped by delivery < 38 weeks, delivery between 38 weeks/1 day and 40 weeks, and delivery > 40 weeks. The authors compared the mean rate of rise in estriol between these groups and found that the groups that delivered earlier had a significantly greater mean rate of rise in estriol. Estriol “plateaued” in patients who delivered after 40 weeks. Interestingly, this study did not show a significant association between absolute concentrations of estriol and time to delivery, which implies that perhaps the rate of change of estriol is more important than the actual level alone. A more robust investigation into the association between decreased E3:P or estriol and induction of labor could help guide patients and providers in shared decision making when planning for inductions, especially as rates of inductions have risen alongside rates of high risk pregnancies and as studies have increasingly demonstrated that elective induction of labor is often a preferred, safe option rather than expectant management for post term pregnancies.[23, 24]

There are, additionally, important considerations to be made when selecting salivary E3:P versus estriol as an outcome measure. Salivary measurements in general may be impacted by environmental factors such as sleep, stress, exercise, oral trauma, and oral intake prior to collection.[25] Concentrations of salivary steroid hormones generally reflect free, unbound, biologically active serum stores.[16] This has been specifically demonstrated for estriol during pregnancy.[26, 27] Salivary progesterone, however, demonstrates more variability over a 24-hour period than serum estriol concentrations and is therefore potentially less diagnostically useful than serum.[16, 28] While E3:P may better capture hormonal interplay mitigating the onset of labor, it is not clear that salivary progesterone is as diagnostically reliable as salivary estriol. Additionally, our study excluded anyone with known factors impacting their salivary hormone levels, but it did not have enough power to ascertain environmental impact on said salivary hormone levels.

Limitations of this study include its small sample size, limited power, and low retention rate. Additionally, we must account for a degree of human error given our study’s significant reliance on participant engagement. For example, multiple patients stopped collecting study samples once they scheduled inductions though they still could have been included in our analysis.

CONCLUSION

Ultimately, there appears to be a potential association between lower E3:P and lack of spontaneous labor that warrants further study, especially as rates of induction of labor continue to rise. Most available research relied on weekly samples to draw conclusions about trends in salivary hormones during term pregnancy. Our study was relatively unique in its use of daily samples, and our findings suggest that meaningful peripartum E3:P patterns may be detected with a larger sample size and a longer data collection period.

Declarations

Ethics approval and consent to participate

Research data supporting this publication was gathered by study investigators with approval from the University of California Irvine Institutional Review Board (study ID 2384) for the purposes of this project and conducted in accordance with the Declaration of Helsinki.

Consent for Publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no declaration of personal or financial competing interests.

Funding

This research received a seed grant from the University of California Department of Surgery.

Authors' contributions

Conception and Study design: CG, MS, LS

Literature Review/Data Acquisition: CG, MS,

Data Analysis and Interpretation: CG, MS, LS

Drafting of the manuscript: CG, MS, LS, ER

Critical revision: LS, ER

Acknowledgements

University of California Irvine Institute for Interdisciplinary Salivary Bioscience

University of California Irvine Institute for Clinical and Translational Science Biostatistics, Epidemiology, and Research Design Unit

Author's Information

Dr. Lourdes Y. Swentek is a board-certified UCI Health surgeon who specializes in trauma, critical care, emergency and general surgery. She earned a medical degree at Loyola University Chicago's Stritch School of Medicine in Maywood, Ill., where she completed a surgical residency. She also completed a residency in general surgery at Loma Linda University Medical Center in Loma Linda, Calif., followed by

fellowship training in trauma and critical care surgery at UCI Medical Center. Dr. Swentek's research interests include the study of inflammatory conditions and acute stress disorders after treatment for traumatic injury.

References

1. Hanley GE, Munro S, Greyson D, Gross MM, Hundley V, Spiby H, et al. Diagnosing onset of labor: a systematic review of definitions in the research literature. BMC Pregnancy Childbirth 2016;16:71.
2. Friedman E. The graphic analysis of labor. Am J Obstet Gynecol 1954;68(6):1568-75.
3. Nassr AA, Berghella V, Hessami K, Bibbo C, Bellussi F, Robinson JN, et al. Intrapartum ultrasound measurement of angle of progression at the onset of the second stage of labor for prediction of spontaneous vaginal delivery in term singleton pregnancies: a systematic review and meta-analysis. Am J Obstet Gynecol 2022;226(2):205-214.e2.
4. 248: Temporal and diagnostic trends of labor and delivery triage visits. American Journal of Obstetrics and Gynecology 2015;212(1, Supplement):S137.
5. Holmes P, Oppenheimer LW, Wen SW. The relationship between cervical dilatation at initial presentation in labour and subsequent intervention. Bjog 2001;108(11):1120-4.
6. Rahnama P, Ziaei S, Faghihzadeh S. Impact of early admission in labor on method of delivery. Int J Gynaecol Obstet 2006;92(3):217-20.
7. Tilden EL, Lee VR, Allen AJ, Griffin EE, Caughey AB. Cost-Effectiveness Analysis of Latent versus Active Labor Hospital Admission for Medically Low-Risk, Term Women. Birth 2015;42(3):219-26.
8. Voegtline KM, Granger DA. Dispatches from the interface of salivary bioscience and neonatal research. Front Endocrinol (Lausanne) 2014;5:25.
9. Darne J, McGarrigle HH, Lachelin GC. Saliva oestriol, oestradiol, oestrone and progesterone levels in pregnancy: spontaneous labour at term is preceded by a rise in the saliva oestriol:progesterone ratio. Br J Obstet Gynaecol 1987;94(3):227-35.
10. Goodwin TM. A role for estriol in human labor, term and preterm. Am J Obstet Gynecol 1999;180(1 Pt 3):S208-13.
11. Kota SK, Gayatri K, Jammula S, Krishna SV, Meher LK, Modi KD. Endocrinology of parturition. Indian J Endocrinol Metab 2013;17(1):50-9.
12. Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Health 2022;6(2):106-115.
13. Heine RP, McGregor JA, Dullien VK. Accuracy of salivary estriol testing compared to traditional risk factor assessment in predicting preterm birth. Am J Obstet Gynecol 1999;180(1 Pt 3):S214-8.
14. Moran DJ, McGarrigle HH, Lachelin GC. Lack of normal increase in saliva estriol/progesterone ratio in women with labor induced at 42 weeks' gestation. Am J Obstet Gynecol 1992;167(6):1563-4.

15. Lachelin GC, McGarrigle HH, Seed PT, Briley A, Shennan AH, Poston L. Low saliva progesterone concentrations are associated with spontaneous early preterm labour (before 34 weeks of gestation) in women at increased risk of preterm delivery. Bjog 2009;116(11):1515-9.
16. Wood P. Salivary steroid assays - research or routine? Ann Clin Biochem 2009;46(Pt 3):183-96.
17. Preterm Labor and Birth: A Clinical Review. MCN Am J Matern Child Nurs 2020;45(6):E23-e24.
18. Committee Opinion No 700: Methods for Estimating the Due Date. Obstet Gynecol 2017;129(5):e150-e154.
19. Smith R, Smith JI, Shen X, Engel PJ, Bowman ME, McGrath SA, et al. Patterns of plasma corticotropin-releasing hormone, progesterone, estradiol, and estriol change and the onset of human labor. J Clin Endocrinol Metab 2009;94(6):2066-74.
20. McGregor JA, Jackson GM, Lachelin GC, Goodwin TM, Artal R, Hastings C, et al. Salivary estriol as risk assessment for preterm labor: a prospective trial. Am J Obstet Gynecol 1995;173(4):1337-42.
21. Heine RP, McGregor JA, Goodwin TM, Artal R, Hayashi RH, Robertson PA, et al. Serial salivary estriol to detect an increased risk of preterm birth. Obstet Gynecol 2000;96(4):490-7.
22. Hedriana HL, Munro CJ, Eby-Wilkens EM, Lasley BL. Changes in rates of salivary estriol increases before parturition at term. Am J Obstet Gynecol 2001;184(2):123-30.
23. Simpson KR. Trends in Labor Induction in the United States, 1989 to 2020. MCN Am J Matern Child Nurs 2022;47(4):235.
24. Grobman WA, Rice MM, Reddy UM, Tita ATN, Silver RM, Mallett G, et al. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. N Engl J Med 2018;379(6):513-523.
25. Schultheiss O, Stanton S. Assessment of salivary hormones. In: E H-J, JS B, editors. Methods in Social Neuroscience. New York, NY: The Guilford Press; 2009. p. 17-44.
26. Lachelin GC, McGarrigle HH. A comparison of saliva, plasma unconjugated and plasma total oestriol levels throughout normal pregnancy. Br J Obstet Gynaecol 1984;91(12):1203-9.
27. Vining RF, McGinley R, Rice BV. Saliva estriol measurements: an alternative to the assay of serum unconjugated estriol in assessing feto-placental function. J Clin Endocrinol Metab 1983;56(3):454-60.
28. Sakkas D, Howles CM, Atkinson L, Borini A, Bosch EA, Bryce C, et al. A multi-centre international study of salivary hormone oestradiol and progesterone measurements in ART monitoring. Reprod Biomed Online 2021;42(2):421-428.

Figures

Sample label	_____
Sample collection date and time	_____
Are you experiencing a NEW onset of any of the following?	☐ my answers are unchanged from yesterday's answers ☐ contractions - regular ☐ contractions - irregular ☐ increased vaginal discharge ☐ ruptured membranes "water broke" ☐ GI symptoms - (constipation or diarrhea) ☐ lower back pain ☐ fatigue ☐ fever ☐ cough ☐ runny nose ☐ cuts/sores/blood in mouth ☐ blood when you brush your teeth or spit in the sink ☐ loose/lost teeth ☐ cavities ☐ none of the above
In the past hour I have	☐ consumed food/drink (including water, candy, chewing gum, cough drops) ☐ consumed coffee ☐ consumed alcohol ☐ consumed dairy ☐ exercised ☐ brushed or flossed teeth ☐ none of the above
Within the last 24 hours have you taken any NEW prescription medications or NEW over-the-counter medications (meaning, medications you started after beginning this study)? Please include medications in any form such as pills, syrups, drops, patches, suppositories, inhalers, creams, ointments, or injections	◯ Yes ◯ No ◯ Unchanged from yesterday
Please list any NEW medications taken within the last 24 hours, including the estimated time you took the medication.	_____
What time did you go to sleep last night?	_____

Figure 1

Daily Participant Survey

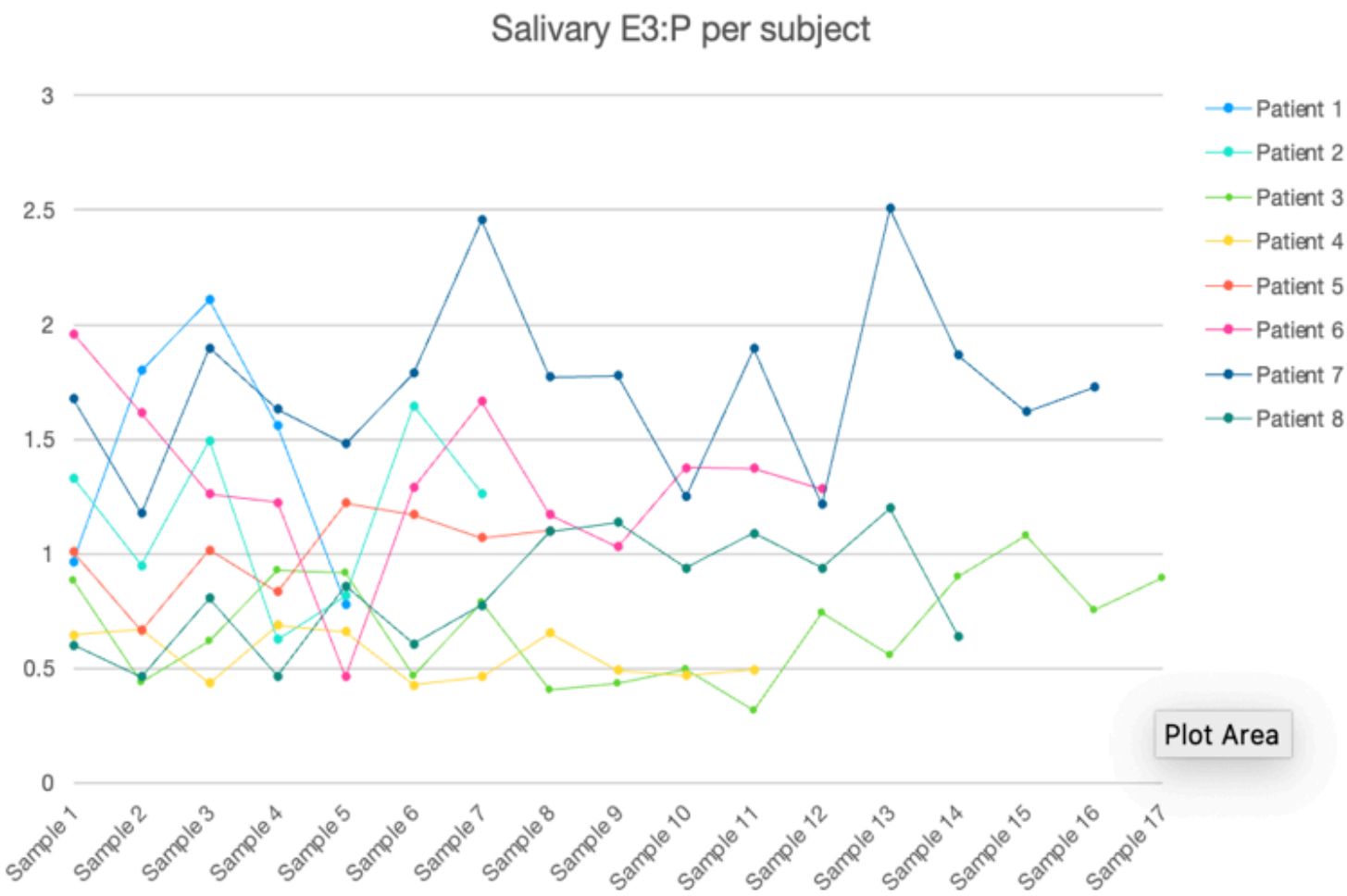


Figure 2

Legend not included with this version.

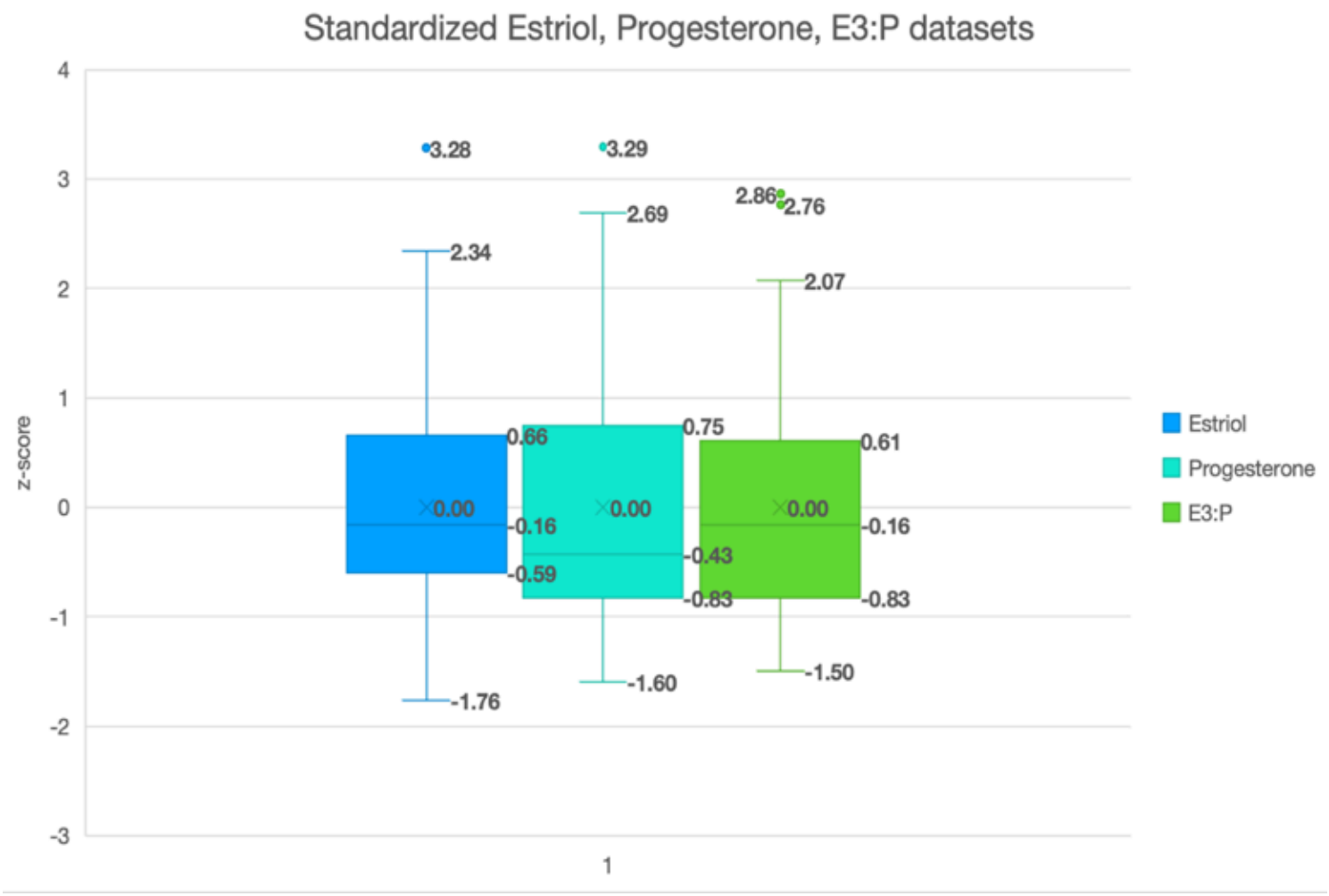


Figure 3

Legend not included with this version.

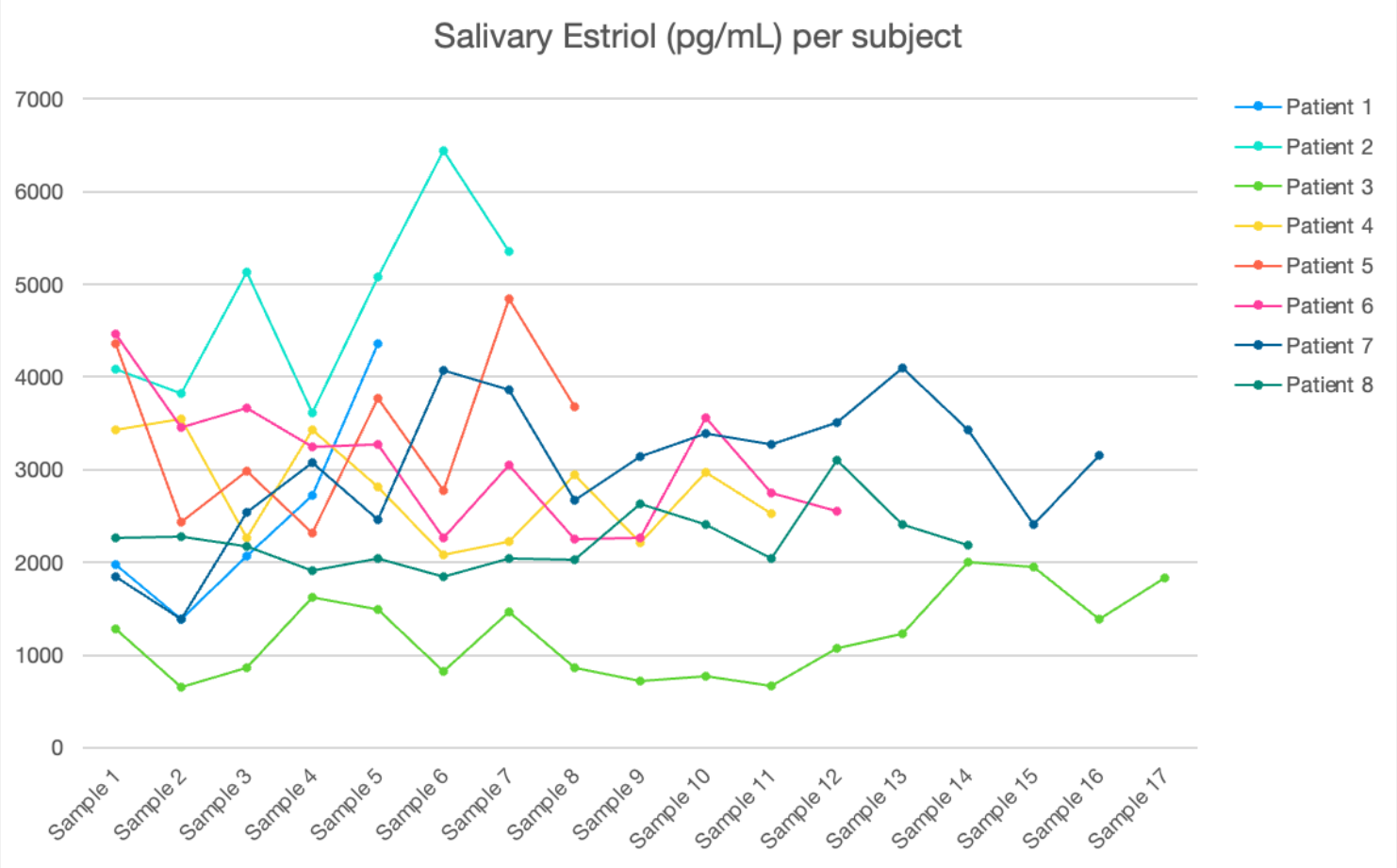


Figure 4

Legend not included with this version.

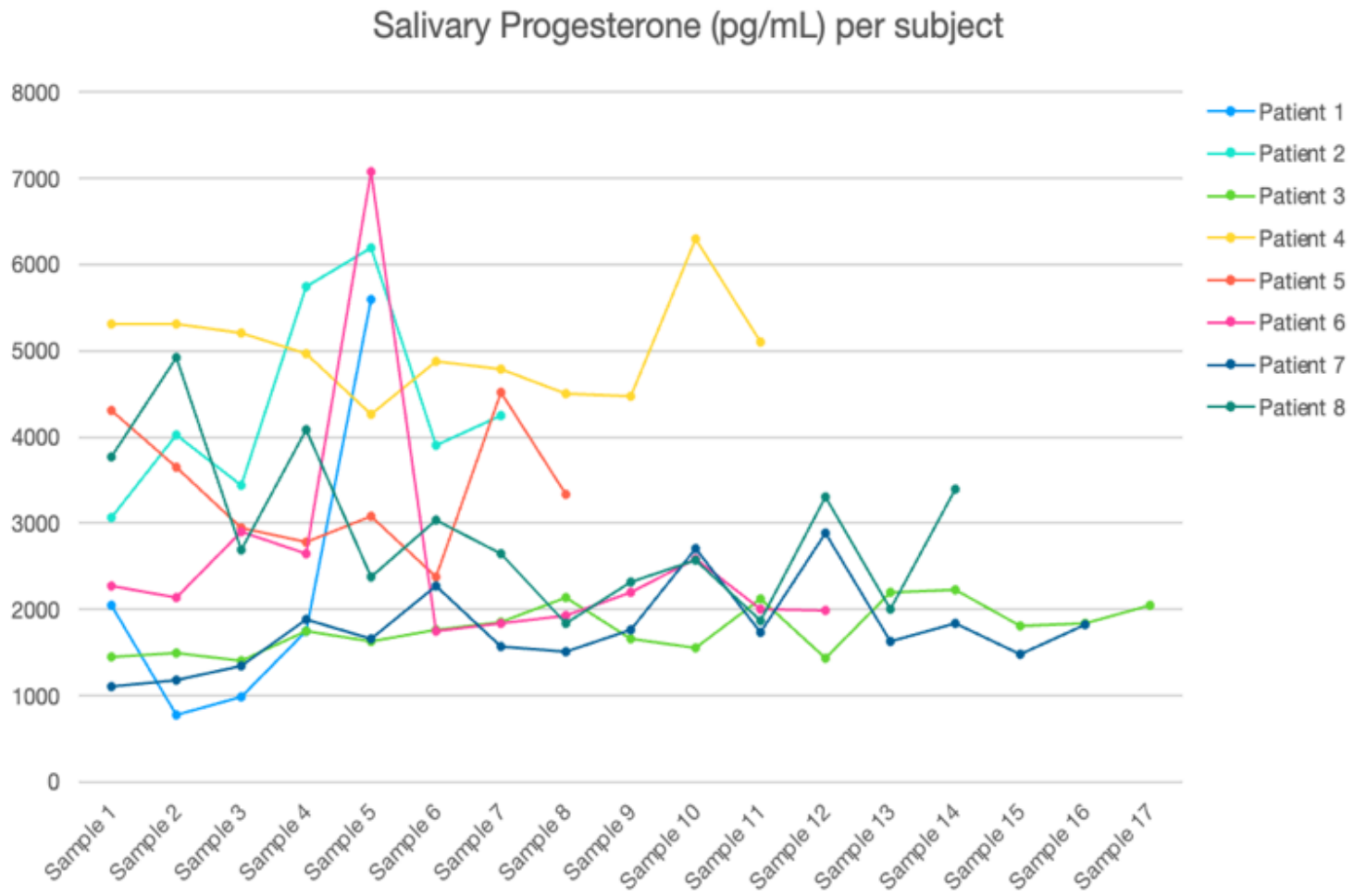


Figure 5

Legend not included with this version.

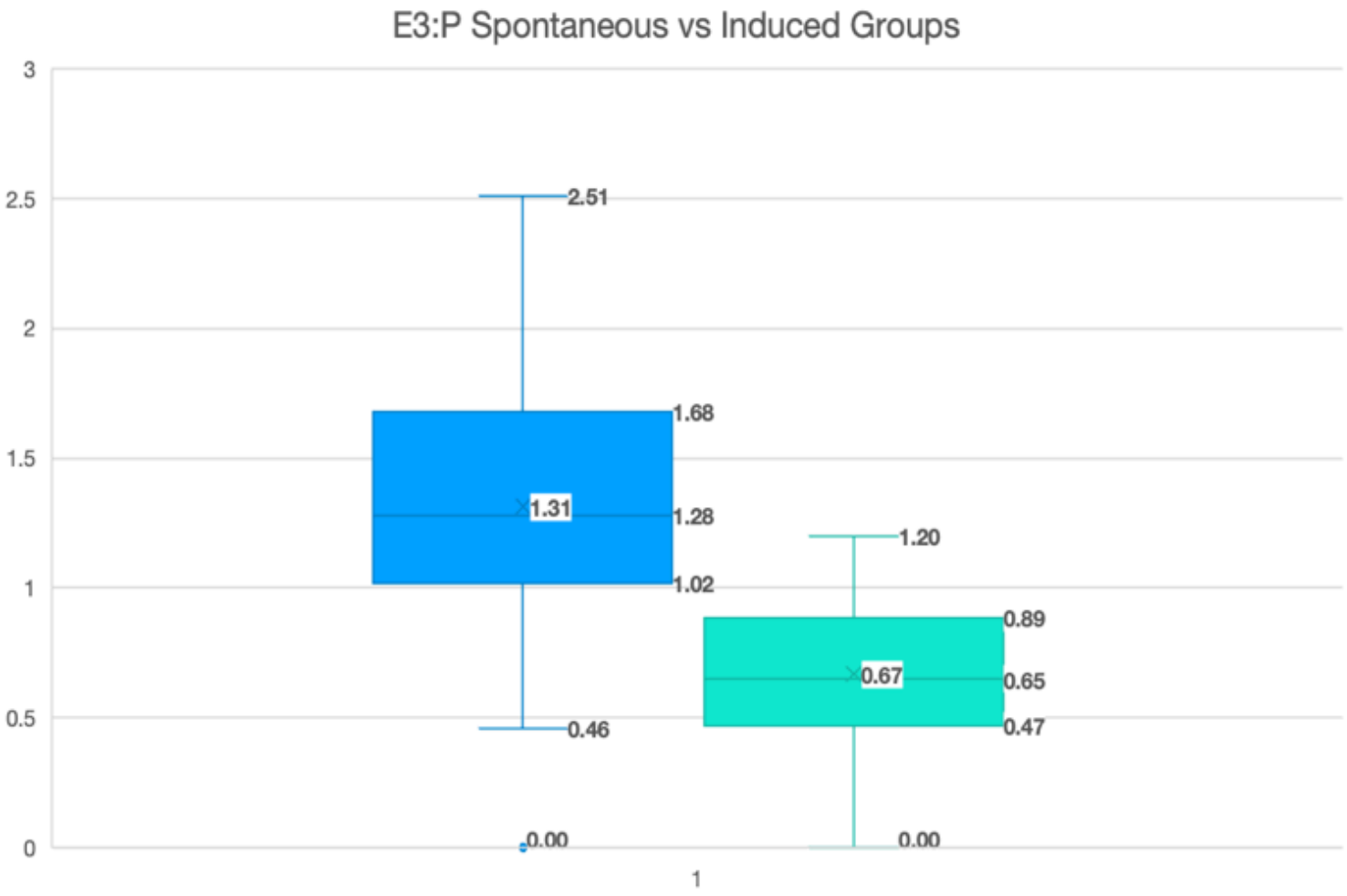


Figure 6

Legend not included with this version.

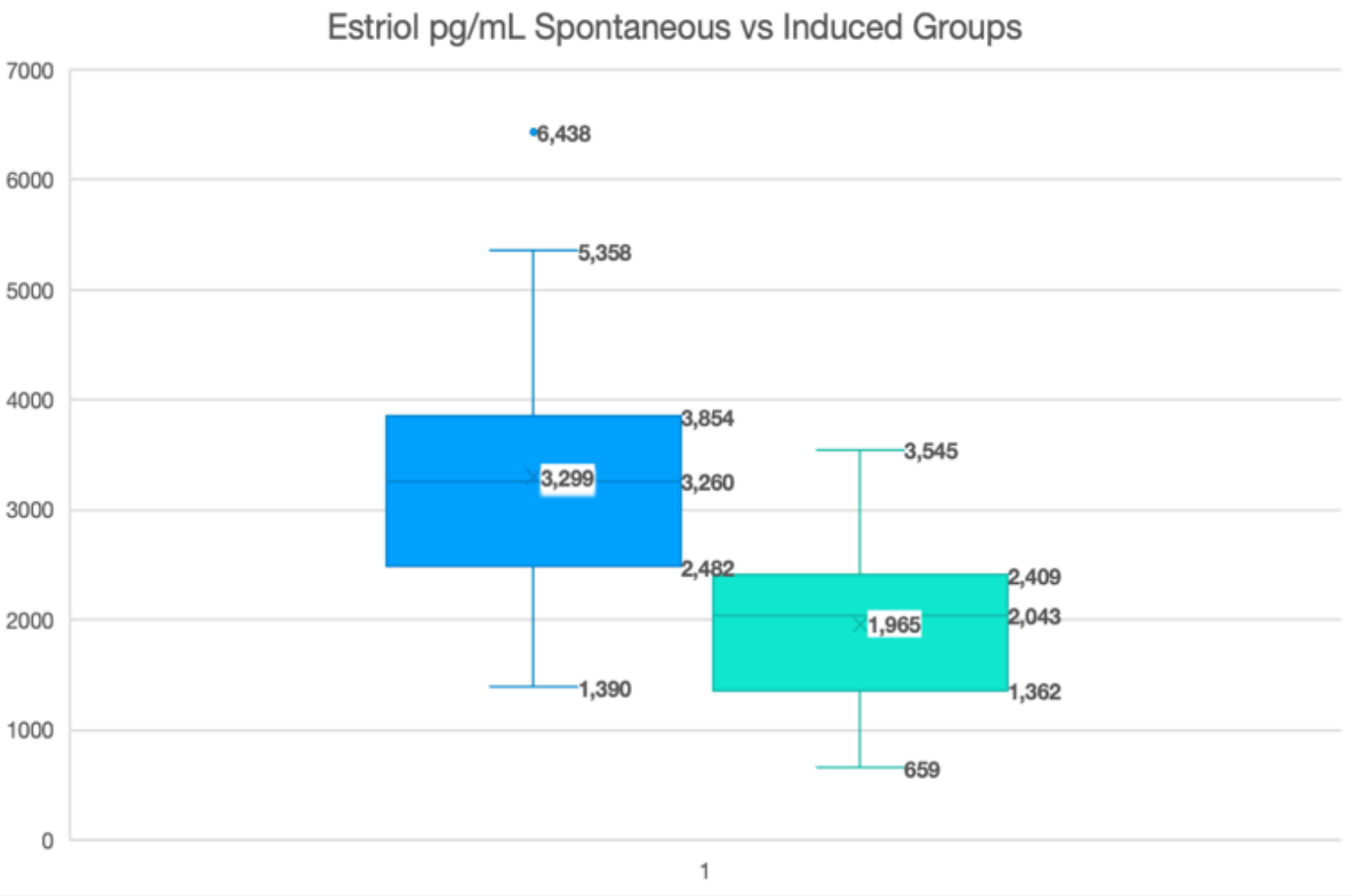


Figure 7

Legend not included with this version.

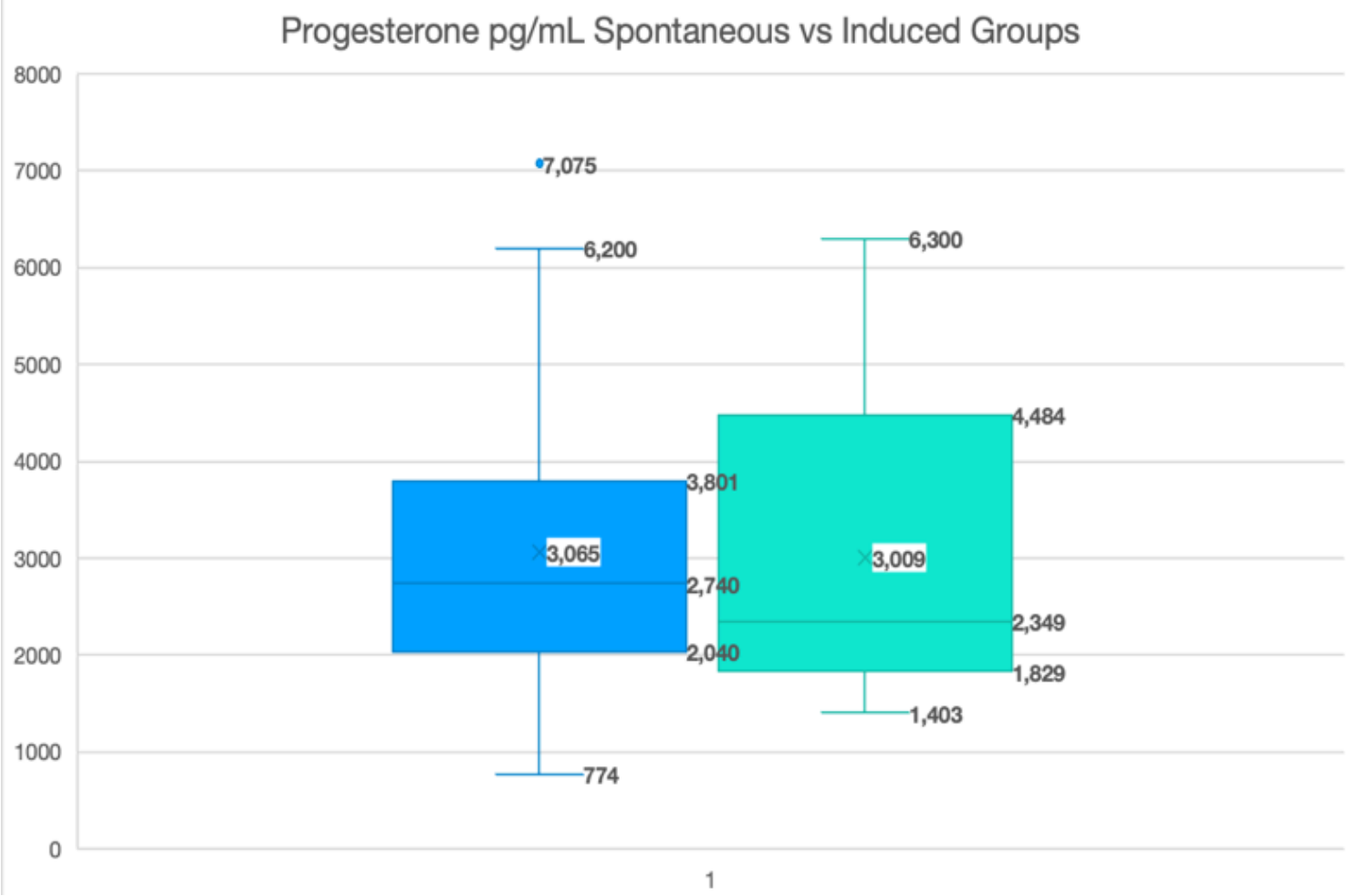


Figure 8

Legend not included with this version.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1toS2.docx