

Relationship between Human Seminal Prostaglandins on Intrauterine Insemination Pregnancy Outcomes

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Abstract

Background: This retrospective cohort study analyzed seminal fluid prostaglandin content and intrauterine insemination (IUI) pregnancy outcomes.

Methods: After an initial recording of semen volume, liquefaction, degree of viscosity and pH, an aliquot (25µL) of semen was loaded onto a disposable counting sperm chamber and evaluated for sperm concentration and motility. An aliquot (0.5-2.0mL) of semen was saved, stored (-80°C) and diluted for PG analysis via a specific ELISA for each prostaglandin (PGF2α, PGE1 and PGE2). Sperm were washed free of seminal fluid via centrifugation (300g) prior to IUI. Prostaglandin content between pregnant and non-pregnant groups was compared by regression analysis and Student's t-test.

Results: A total of 49 semen samples were evaluated as described. The overall IUI pregnancy rate was 24.5%. Patients who became pregnant had a lower PGE1:PGE2 ratio (5.95pg/mL vs 9.06pg/mL) and lower PGF2α content (1770.12pg/mL vs 2381.71pg/mL) than those that did not become pregnant, respectively.

Conclusions: The preliminary findings suggest that the PGE1:PGE2 ratio may be important for pregnancy potential but not sperm motility. PGF2α content may not influence sperm motility as it does with pregnancy outcomes. Additional studies are warranted to determine the optimal ratio and content of the prostaglandins to ensure sufficient sperm motility, transport, and subsequent fertilization for a successful pregnancy outcome.

Keywords: Seminal prostaglandins; Intrauterine insemination; IUI; Pregnancy outcomes

Introduction

Mammalian semen consists of spermatozoa and accessory glands fluid secretions which promote sperm survival, motility, and overall male fertility [1]. A primary component of seminal fluid is prostaglandins (PG), which have a dual role: facilitation of sperm transport within the female reproductive tract via induction of peristaltic contractions, and induction of sperm motility [2,3].

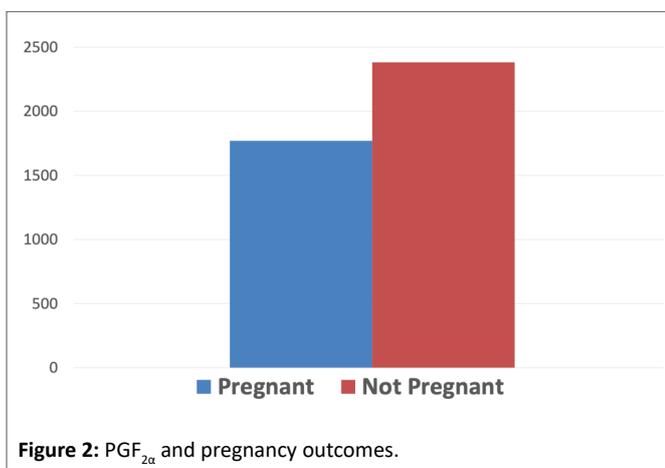
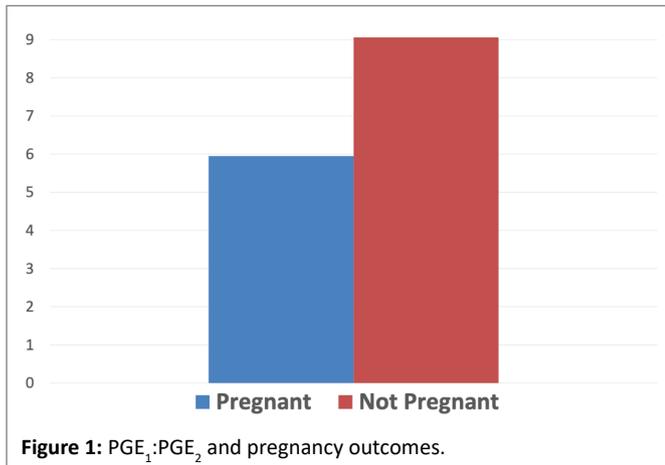
Of the many forms of prostaglandin noted in human male semen, PGF2α, PGE1, and PGE2 have been extensively studied in humans [4,5]. Each prostaglandin seems to play a slightly different role in this complex process. Previous data from both fertile and infertile men indicate that male factor infertility can result from individual PG levels that are either too high or too low [6].

PGF2α is primarily associated with induction of peristaltic contractions within the female reproductive tract, which assists with propagation of spermatozoa toward their ultimate destination, i.e.

the ampullary-isthmus junction [7,8]. Interestingly, high levels of PGF2α have been measured in the cervical mucus of women who utilize an intrauterine device (IUD) for contraception [9]. It has been suggested that high enough PGF2α levels in these women may further contribute to inactivation of sperm motility, providing another means of preventing pregnancy while utilizing an IUD [10].

PGE1 and PGE2 are primarily associated with sperm motility [11]. Studies have demonstrated the effect that these specific prostaglandins have on spermatozoan ability to move effectively in a manner that is generally accepted to be necessary for natural fertilization of an ovum [12]. Satisfactory spermatozoa motility also remains necessary for successful fertilization in methods of assisted reproduction that do not involve intracytoplasmic sperm injection (ICSI), such as during intrauterine insemination (IUI).

Intrauterine insemination involves direct introduction of a washed, concentrated sperm sample directly to the uterus. It bypasses the step



of needing to be transported through the vagina and cervix within seminal fluid in order to reach the uterus. Washing the sample of seminal fluid prior to introduction effectively minimizes the peristaltic effect that a woman's reproductive tract would normally undergo in response to seminal fluid since the seminal prostaglandins are no longer present.

IUI success can be affected by numerous factors, including female anatomy, age of the female patient, duration of infertility, type of infertility, cause of infertility (male, female, combined or unexplained), stimulation protocol, follicular response, and endometrial thickness [13]. In this study, we looked specifically at seminal prostaglandins as a male factor potentially contributing to success or failure in this multi-faceted procedure.

The composition of seminal fluid from different men differs in makeup across a number of analytes [14]. While not completely understood, the reasons for these differences may be linked to differences in donor genetics, diet, and activity level prior to sample delivery [15,16]. Furthermore, discrepancies between samples provided by the same donor on a different day or time of day have been noted.

Studies have demonstrated the lower physiological levels of PGE2 and PGF2α that still exist within normal range have been shown to improve human sperm functions [17]. We hypothesized that there would be a significant difference in seminal prostaglandin levels of samples successfully leading to pregnancy. The purpose of this pilot

study was to analyze prostaglandin PGF2α content and PGE1: PGE2 ratios among successful *versus* unsuccessful pregnancy as primary outcome following intrauterine insemination.

Materials and Methods

This study was a retrospective cohort review of seminal prostaglandin content and ratios among successful *versus* unsuccessful pregnancies following IUI procedure. A total of 49 semen samples were evaluated in the manner described as follows. After an initial recording of semen volume, liquefaction, degree of viscosity and pH an aliquot (5μL) of semen was loaded onto a disposable counting sperm chamber and evaluated for sperm concentration and motility. Sperm were washed free of seminal fluid *via* centrifugation (300g) prior to IUI. An aliquot (0.5-2.0mL) of semen was saved, stored (-80°C) and diluted (1:10 with Tris buffered saline) for PG analysis *via* a specific ELISA for each prostaglandin: PGF2α ELISA Kit Catalog Number ADI-900-069; PGE1 ELISA Catalog No. ADI-900-005; and PGE2 ELISA Kit Catalog Number ADI-900-001. The PG ELISA kits (separate commercially available kits for each PG) are a competitive immunoassay for the quantitative determination of PGE1/PGE2/PGF2α in biological fluids, i.e. semen. Each PG kit (Enzo Life Sciences, Farmingdale, NY) uses a specific polyclonal antibody for each PG molecule to bind, in a competitive manner, the specific PG in the sample (triplicates) or an alkaline phosphatase molecule which has the specific PG covalently attached to it. After a simultaneous incubation for 5 minutes at room temperature the excess reagents are washed (Tris buffered saline containing detergents) away and substrate is added. After 45 minutes of incubation time the enzyme reaction is stopped (trisodium phosphate in water) and the yellow color generated read on a microplate reader (Microwash+ Microplate washer, Molecular devices, Sunnyvale, CA) at 405nm. The intensity of the bound yellow color is inversely proportional to the concentration of the respective PG standards (PGE1, 4.88pg/m-5,000pg/mL; PGE2, 39.1pg/mL-2,500pg/mL; PGF2α, 3.05pg/mL-50,000pg/mL) or samples. The measured optical density is used to calculate the concentration for each specific prostaglandin, PGE1/PGE2/PGF2α.

Prostaglandin content between pregnant and non-pregnant groups was compared by regression analysis and Student's t-test. Data on patient demographics, e.g. time of day of sample production, or other factors affecting the samples were not investigated for purposes of this study.

Results

The overall IUI pregnancy rate was 24.5%. As illustrated in Figure 1, patients who became pregnant had an overall lower seminal PGE1:PGE2 ratio (5.95pg/mL *vs* 9.06pg/mL) compared to those that did not become pregnant, respectively. Figure 2 illustrates that patients who became pregnant had an overall lower seminal PGF2α content (1,770.12pg/mL *vs* 2,381.71pg/mL) compared to those that did not become pregnant, respectively. Sensitivity for each prostaglandin is as follows: PGE1, 5.58pg/mL; PGE2, 13.4pg/mL; and PGF2α, 6.71pg/mL. Coefficient of variability for each prostaglandin is as follows: PGE1, 9.5%; PGE2, 13.58%; and PGF2α, 6.8%.

Discussion and Conclusion

Human fertility is a complex topic influenced by several major factors related to both male and female components. About half of all cases of infertility are found to be "male factor" in origin [18]. As the medical community continues to learn more about fertility and the factors that affect ability to achieve pregnancy, questions about the role of more minor factors, such as prostaglandins, arise.

Prostaglandins are known to play a diverse collection of roles in mammalian physiology across a multitude of body systems [19]. Not surprisingly, this extends to human reproduction physiology [20]. In addition to numerous other roles and perhaps many we are not yet aware of, prostaglandins are responsible for helping facilitate delivery of sperm to ovum for fertilization by means of peristaltic contractions of the female reproductive tract, as well as activation and support of sperm motility [8]. We are now learning more about the role that prostaglandins play by means of acting directly on male spermatozoa. Previous research has demonstrated the impact that prostaglandins have on human sperm function with regards to motility [10]. Findings by Rios, et al. [17] showed that incubation with low physiological levels of PGE2 or PGF2 α increased sperm function. They posited that their findings might be useful in application toward assisted reproduction technologies (ART).

Results from this pilot study do suggest that both the concentration and ratio of seminal prostaglandins may be linked to the pregnancy potential of the spermatozoa used in intrauterine insemination. Since sperm motility significantly impacts IUI outcomes [21] and that prostaglandins impact sperm motility [10,22] and transport through the female reproductive tract [8] these finding may help explain the role prostaglandins have on IUI outcomes. Our preliminary findings seem to point toward an association between improved IUI pregnancy outcomes and a lower PGF2 α concentration as well as with a lower PGE1: PGE2 ratio. This study does not provide additional insight into the effect that these prostaglandin levels or ratios may have on sperm motility since motility was not being measured aside from the general satisfaction parameters necessary in order to proceed with IUI.

While this information is promising for better understanding the role prostaglandins play in reproductive potential, additional studies are warranted to determine the optimal ratio and content of seminal prostaglandins to ensure sufficient sperm motility, transport, and subsequent fertilization for a successful pregnancy outcome. We are also hopeful that further research into these questions may lead us to a better understanding of why seminal prostaglandin levels differ across males and samples given, as well as interventions that impact seminal prostaglandins, and how to optimize levels prior to attempting pregnancy. Perhaps further research may ultimately lead to improving fertility outcomes in both ART and patients trying to conceive without assistance.

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