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Next Generation Lubricants and Their Potential Use in Fertility Treatment

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Abstract

While generally recognized as a potential source of contamination during the collection process, lubricants are often used at the preference of the male partner to prevent irritation. While older lubricants have been studied, there is currently no conscience within programs as to what constitutes a "safe" lubricant. The object of the current study was designed to evaluate chemically unique "next generation" lubricants in comparison to lubricants currently in use in fertility treatment and/or recognized as fertility safe; the first was a silicone-based lubricant, the second is a water-based, plant-based organic compound, in comparison to two established medical lubricants and a control. Twelve deidentified semen samples from the clinical andrology laboratory were used to test the lubricants following semen analysis. In order to enter the study, the sample had to have a minimum of 30×10^6 motile cells. Samples were then processed using a simple sperm wash modified to reconstitute the pellet into a final volume of 7 mL. Half-milliliter aliquots were then transferred into 13 wells of a standard 24-well culture plate. One well was used as a control. The remaining wells received one of the four lubricants at one of three volumes (10, 50, or 100 uL), producing 12 treatment combinations (four lubricants + 3 concentration levels) and the control. The samples were then cultured at room temperature for 24 hours. At times 0, 1, 3, 12, and 24 hrs, the plate was agitated to remix the sample, and a 4 uL aliquot of each well was analyzed for standard semen parameters using a computer-assisted semen analyzer. Results indicated the expected decrease in semen parameters over time in all treatments ($P < 0.001$). There was also a dose-dependent drop in most of the lubricants. However, samples contaminated with the newer lubricants appeared to maintain semen parameters similar to the controls at all but the 100 ul level of contamination, while the older lubricants caused decreases in sperm function at much lower concentrations. While semen parameters alone should not be the only criteria for the selection of a lubricant,

the present study suggests newer formulations of lubricant are less likely to interfere with sperm function.

Keywords

Lubricants, Fertility, Contamination, Next-Generation

1. Introduction

Sexually active couples trying to conceive often choose to use lubricants for a variety of reasons, including vaginal dryness and dyspareunia [1] [2]. When used during intercourse, a number of these lubricants have been demonstrated to have negative impact on both sperm motility and fertility outcomes

Further, a number of studies have shown one in three couples seeking infertility counseling can be attributed to male factor infertility and may involve the need for semen collection as part of treatment. The emotional stress of being unable to conceive a child and the environmental stress of being in a physician's office can make it difficult for men to produce a semen sample. Therefore, men undergoing infertility studies are commonly offered lubricants to aid in masturbation. Nearly 75% of men prefer to use lubricant during semen collection for a fertility evaluation, and more than half prefer to use lubricant during collection [3]. However, there are unclear guidelines for medical professionals regarding lubricants that are safe for couples trying to conceive.

Both standard semen analysis and more advanced testing, such as DNA fragmentation, used to determine sperm function, have demonstrated the deleterious effects vaginal lubricants can have on sperm integrity [3]-[9]. Many of these effects are seen in common lubricants such as K-Y Jelly, Replens, and Astroglide [3] [10]. Even lubricants that are not labeled "non-spermicidal" have the potential to cause damage to sperm. This can lead to couples choosing a lubricant that may, in fact, inhibit their ability to become pregnant even when using "non-spermicidal" options. Further, it is essential to note that "organic" substances such as olive oil and saliva have also been associated with significantly reduced progressive motility parameters [10] [11]. With all the deleterious effects caused by many lubricants, it is understandable how challenging it may be for providers to recommend a safe lubricant.

Many lubricants have not been tested to determine if they are sperm-friendly, and numerous lubricants labeled "sperm friendly" can have destructive effects on sperm. There is no standard lubricant recommended by fertility experts that is safe for semen collection or sexual intercourse when trying to conceive, and the current "gold standard" on the market for semen collection has not been tested for sperm safety. The current study aimed to compare a medical lubricant, a lubricant designed for fertility, both in use in fertility clinics to a new silicone lubricant and a new organic, water-based lubricant which have not been previously assessed for fertility treatment.

2. Materials and Methods

To assess these new lubricants, semen samples were obtained from a clinical fertility lab following routine semen analysis. Patients seeking a diagnostic semen analysis were advised to abstain from sexual intercourse for a period of 48 - 72 hours prior to collection of the sample for analysis. Samples were collected at the laboratory into standard specimen cups by masturbation and then analyzed using standard clinical lab protocols. Once the clinical analysis was completed samples that met the inclusion criteria (see below) were transferred to the research lab under an exempt IRB protocol. The protocol allowed non-fertilization experiments with semen samples following clinical analysis. To ensure all ethical concerns over patient confidentiality, the IRB protocol required the clinical lab to deidentified the sample prior to handing them off to the research lab making them "deidentified tissue samples". Once the clinical semen analysis was completed, samples potentially meeting the inclusion criteria were transferred to an unlabeled test tube to effectively deidentify them prior to their transfer to the research laboratory. The research lab received only the sample and the knowledge it might meet the inclusion criteria; no additional data was provided nor was any experimental data returned to the clinical lab.

Once transferred to the research laboratory, the samples underwent a second semen analysis consisting of a manual volume determination and an automated semen analysis using a Hamilton Thorn Computer Assisted Semen Analyzer (CASA) unit to ensure the inclusion criteria were met. To enter the study, the samples had to meet minimum criteria of 30 million motile cells to ensure a minimum final concentration of 4 million cells per well (treatment) or the equivalent of 8 million cells per milliliter. Well within the detection limits of the CASA unit. A total of 12 samples were transferred from the clinical lab to the research lab during the study period. All met the inclusion criteria.

Following the initial research analysis, 2 mL of Multi-Purpose Handling Medium-Complete (MHM-C; FUJIFILM Irvine Scientific Inc., Santa Ana, CA) was added to the test tube and vortexed for 10 - 15 seconds. The samples were then centrifuged at 1600 revolutions per minute for 6 minutes to form a pellet. The supernatant was discarded, and the sperm pellet was diluted with 7 mL of MHM-C and vortexed for 10 - 15 seconds for resuspension. Half-milliliter aliquots of the cell suspension were transferred to thirteen wells of a Falcon 24-well Cell Culture Plate (Corning Inc., Corning, NY). Wells to be used for lubricant contamination were prepared by removing a portion of the cell suspension and replacing it with an equal volume of the lubricant compound at doses of: 10 (low contamination—2% by volume), 50 (moderate contamination 10% by volume), or 100 μL (high contamination—20% by volume) of one of the four lubricants. Once the lubricant was added the solution was gently aspirated in a disposal pipette to mix the lubricant into the cell suspension. While the exact formulation of each lubricant is a proprietary trade secret, they can be described as: Treatment A) Pre-Seed Fertility-Friendly Lubricant (Church & Dwight Co., Inc, Ewing, NJ)—a

"Fertility friendly" lubricant design to be pH balanced and isotonic with the vaginal environment to promote sperm health (Fertility), Treatment B) Henry Schien Lubricating Gel (Henry Schien Inc., Melville, NY)—a standard medical lubricant that is water soluble, orally nontoxic and primarily designed for use with rectal/vaginal medical devices (Standard), Treatment C) Überlube, (Überlube, Chicago, IL)—a silicone based lubricant developed for sexual intimacy (Silicone) or Treatment D Fav Whet Plant-Based Sex Serum (Personal Fav Co., Los Angeles, CA)—water base, plant extract based lubricant designed primarily to increase sexual intimacy (Natural). The final well remained untouched as a control. Once prepared, the culture plate was incubated at room temperature and stored in a dark area.

At hours 0, 1, 3, 12, and 24, 4 µl from each sperm and lubricant combination were pipetted and placed on a 37˚C Leja Slide Semen Analysis Chamber (Spectrum Technologies, Healdsburg, CA) and analyzed using a Hamilton Thorne Integrated Visual Optical System (IVOS) sperm analyzer. The following variables were recorded for each of the samples: total concentration (M/ml), motility (%), rapid cells (%), path velocity (VAP, µm/s), track speed (VCL, µm/s), lateral displacement (ALH, µm), straightness (STR, %), progressive velocity (VSL, µm/s), elongation (%), beat cross frequency (BCF, Hz), and linearity (LIN, %).

As the goal of the study was to determine the effects of increasing lubricant contamination on sperm function, the original analysis was a 2-way independent analysis of the variance of each lubricant compared to the control with repeated measures over time using a P value of $P < 0.05$ or below as significant. In cases where results were significant for treatment (lubricant concentration), data were reanalyzed using a one-way analysis and Tukey's mean separation to establish the concentration of lubricant necessary to decrease motility in comparison to the control.

3. Results

There were significant differences in all of the motile parameters measured by the CASA unit ($P < 0.0230$). However, because of its universal acceptance as a measurement of sperm quality, results here will focus on the percentage of motility across the 24-hour period of observation and the effects of the varying levels of contamination of the four lubricants used in this study. Further, while the motility in control samples remained fairly stable across the 24-hour testing period ($P = 0.381$), there were significant differences in the reaction of the cells exposed to the lubricants ($P < 0.001$).

The four lubricants can be thought of as falling into four distinct classes. The Henry Shien lubricant is a standard water-based lubricant, used in a number of medical procedures, and thought of as "safe" for contact with external body surfaces (Standard). The Pre-Seed is a self-described "Fertility Friendly" (Fertility). Überlube a Silicone-based compound—untested in fertility (Silicone), and the Fav lubricant—an "all-natural", water-based lubricant consisting of plant extracts designed for couple intimacy and untested for fertility use (Natural).

As might be expected from the diverse set of compounds, there were significant differences in motility based on compound ($P < 0.001$) and level of exposure ($P < 0.001$). Some lubricants had immediate effects at the lowest levels of exposure, while others appeared to have no or even a positive effect on sperm motility across the 24-hour incubation period. Because of the large number of comparisons being made (13 compound/exposure combinations × 5-time points = 85 compound combinations, data have been graphically presented for each of the five time points).

The standard lubricant appeared to have deleterious effects on motility at the 0 hr time point (CASA testing within 5 minutes of exposure; Figure 1). Decreases were seen in motility in all samples exposed to moderate (10% by volume) and highest levels (20% by volume) of lubricant contamination. Both the Fertility Friendly and Natural lubricants appeared to interfere with motility at the highest levels of contamination, while the Silicone based lubricant appeared to have no detrimental effect on the sample motility, even at the highest levels of contamination, compared to the control.

By one hour, even cells exposed to the lowest levels of contamination of the Standard lubricant were demonstrating decreased motility (Figure 2; $P < 0.001$). There was also a decrease in motility in cells exposed to moderate and high levels of contamination of the Fertility-Friendly lubricant. However, after one hour of exposure cells exposed to the Silicone or Nature Lubricants had equal levels of motility to the control regardless of the concentration of the lubricants in the media.

After three hours of exposure, cells exposed to either the Standard lubricant or the Fertility friendly lubricant demonstrated decreased motility at all three levels of exposure. Cells exposed to the lowest two levels of contamination with the

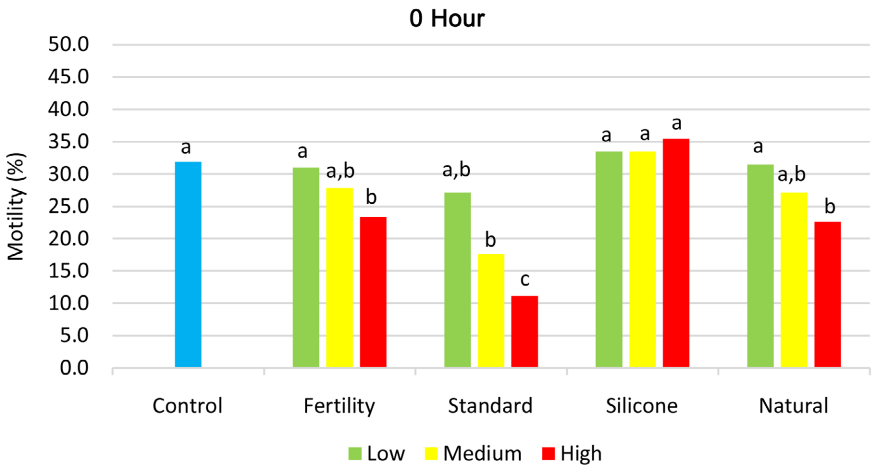

Figure 1. The immediate effects of cell exposure to a series of lubricant compounds at varying concentrations (0, 10, 50 or 100 µL) on sperm cell motility in culture, including a "Fertility friendly" lubricant (Pre-Seed Fertility-Friendly Lubricant), a Standard medical lubricant (Henry Schien Lubricating Gel), a Silicone based lubricant (Überlube), or Natural water-based, plant-based lubricant (Fav Whet Plant-Based Sex Serum). Bar with differing superscripts are different ($P < 0.001$).

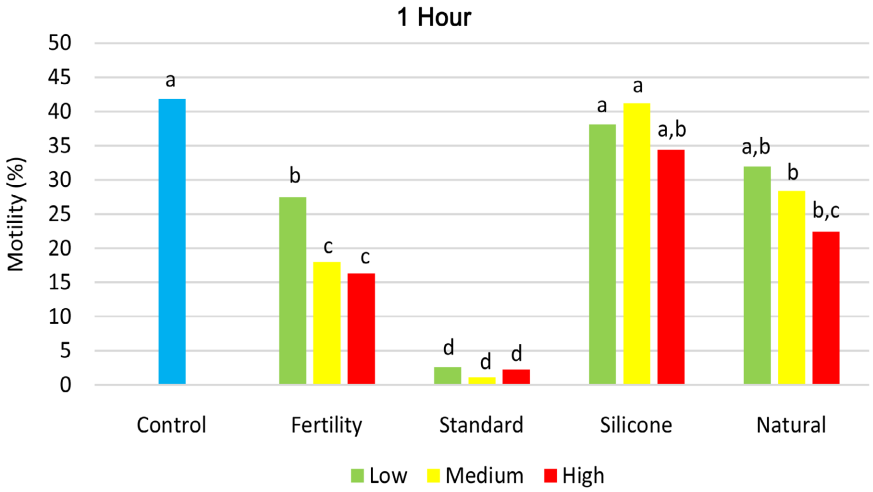

Figure 2. Motility of human sperm samples following 1 hour's exposure to a series of lubricant compounds at varying concentrations (0, 10, 50 or 100 µL) on sperm cell motility in culture, including a "Fertility friendly" lubricant (Pre-Seed Fertility-Friendly Lubricant), a Standard medical lubricant (Henry Schien Lubricating Gel), a Silicone based lubricant (Überlube), or Natural water-based, plant-based lubricant (Fav Whet Plant-Based Sex Serum). Bar with differing superscripts are different ($P < 0.001$).

Natural lubricant (2% and 10% by volume) continued to demonstrate motilities similar to the control, while the motility of cells contaminated with the highest contamination were higher than the motility of cells exposed to any level of the Standard or Fertility Friendly lubricants. Interestingly the cells exposed to the Silicone lubricant had equivalent or higher motilities compared to the control at all three levels of exposure (**Figure 3**; $P < 0.001$).

By twelve hours, the cells exposed to the standard lubricant were essentially non-motile (**Figure 4**; $P < 0.001$). Cells exposed to any level of the Silicone lubricant continued to demonstrate motilities similar to the control, as did cells exposed to the lowest level of the natural lubricant. The cells exposed to the lowest levels of the Fertility Friendly maintained motilities similar to cells exposed to the higher levels of the natural lubricant.

As mentioned above, the control group's motility was essentially the same across the 24-hour observation period, as was motility in cells exposed to the lower two levels of the Silicone lubricant and the lowest level of the natural lubricant. However, by 24 hours of exposure, the cells exposed to the highest levels of the Silicone lubricant we below the control but still higher than any group exposed to the standard or Fertility Friendly lubricants (**Figure 5**).

4. Discussion

The objective of this study was to compare "newer" lubricant options with those currently in use, including those marketed as "fertility-friendly" and "organic, plant-based". Lubricants are employed in a diverse range of fertility-related situations, encompassing coitus, semen collection, and ultrasound, among others. Despite their widespread usage, a considerable number of couples and medical

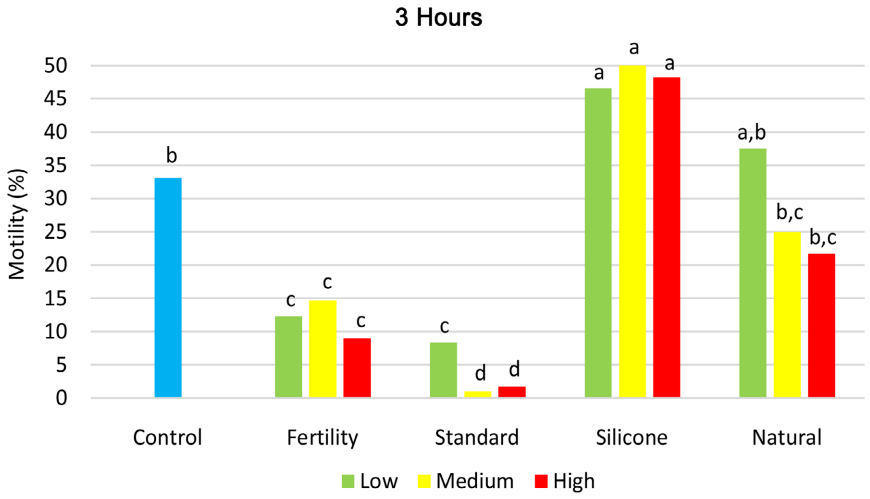

Figure 3. Motility of human sperm samples following 3 hour's exposure to a series of lubricant compounds at varying concentrations (0, 10, 50 or 100 µL) on sperm cell motility in culture, including a "Fertility friendly" lubricant (Pre-Seed Fertility-Friendly Lubricant), a Standard medical lubricant (Henry Schien Lubricating Gel), a Silicone based lubricant (Überlube), or Natural water-based, plant-based lubricant (Fav Whet Plant-Based Sex Serum). Bar with differing superscripts are different ($P < 0.001$).

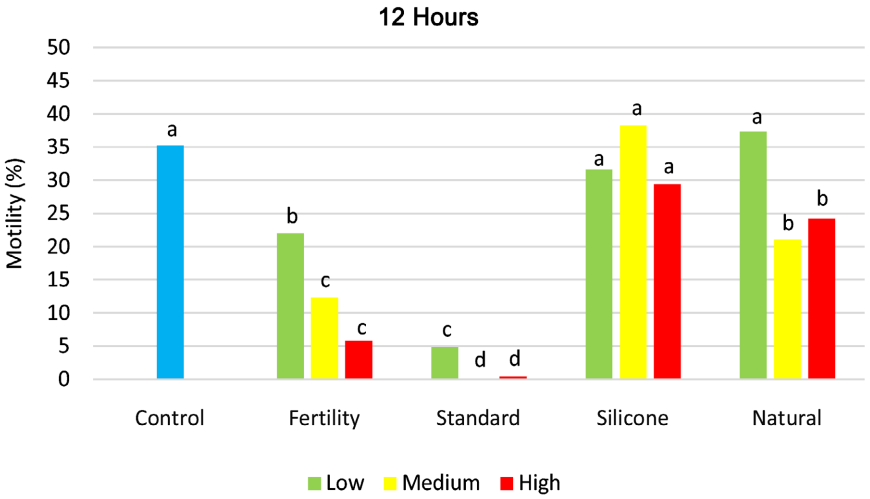

Figure 4. Motility of human sperm samples following 12 hour's exposure to a series of lubricant compounds at varying concentrations (0, 10, 50 or 100 µL) on sperm cell motility in culture, including a "Fertility friendly" lubricant (Pre-Seed Fertility-Friendly Lubricant), a Standard medical lubricant (Henry Schien Lubricating Gel), a Silicone based lubricant (Überlube), or Natural water-based, plant-based lubricant (Fav Whet Plant-Based Sex Serum). Bar with differing superscripts are different ($P < 0.001$).

practitioners remain unaware of the potential adverse impact that certain lubricants can have on sperm quality [5] [6]. Semen collection can be a stressful experience for men, which can cause a challenge in producing a sample within a clinic setting [12]. Due to this, lubricant is highly requested for masturbation, [3] but there is no standard guidance provided to physicians on which lubricant is sperm safe. The current study showed an undeniable decrease in sperm motility

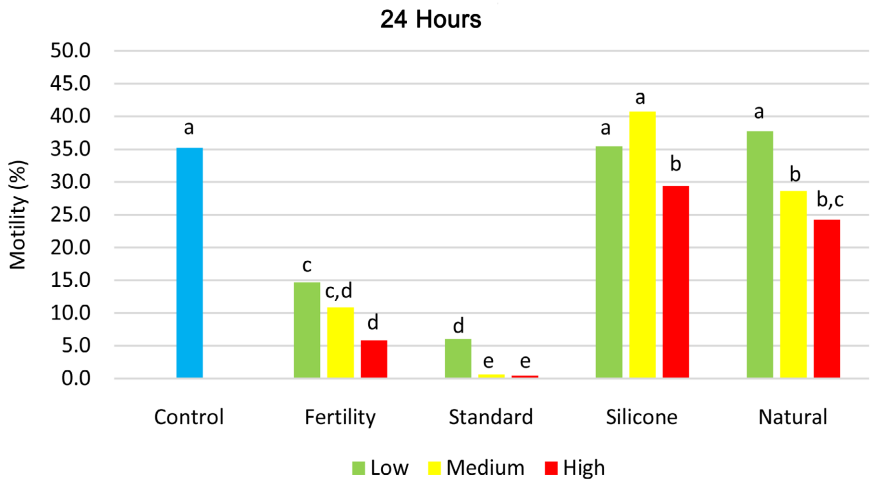

Figure 5. Motility of human sperm samples following 24 hour's exposure to a series of lubricant compounds at varying concentrations (0, 10, 50 or 100 µL) on sperm cell motility in culture, including a "Fertility friendly" lubricant (Pre-Seed™ Fertility-Friendly Lubricant), a Standard medical lubricant (Henry Schien Lubricating Gel), a Silicone based lubricant (Überlube), or Natural water-based, plant-based lubricant (Fav Whet Plant-Based Sex Serum). Bar with differing superscripts are different ($P < 0.001$).

as early as one hour with both the Henry Schien Lubricant Gel (standard) ($P < 0.001$) and Pre-Seed™ Fertility-Friendly Lubricant. Conversely, Überlube (Silicone based), did not interfere with sperm motility over a 24-hour period ($P = 0.643$).

Neither the Henry Schien Lubricant Gel nor Überlube has undergone previous investigations. Notably, even at the minimal concentration of five microliters, the Henry Schien Lubricant Gel exhibited the lowest percentage of motile sperm across all experimental groups, demonstrating a precipitous decline in sperm motility as the lubricant concentration increased. These findings have significant implications for the fertility community considering the widespread use of the Henry Schien Lubricant Gel with instrumentation. Likewise, the Pre-Seed Fertility-Friendly Lubricant showcased a decrease in motility at moderate and high concentrations. This aligns with the observations made by Markram *et al.*, [5] which highlighted a decline in sperm forward progression upon treatment with Pre-Seed™. In contrast, other investigations have reported no toxic effects on sperm when employing Pre-Seed [3] [4] [7] [8]. However, due to the conflicting nature of the available data, further investigations are necessary before recommending Pre-Seed as a "fertility-friendly" lubricant for couples attempting to conceive.

While it can be argued that cells used in various assisted reproductive procedures would not be exposed to the lubricants for the extended periods described in these experiments. It is important to point out that some lubricants, such as the Standard lubricants, are used in auxiliary procedures such as ultrasound procedures which potentially could be left as a residue within the vagina. Further, lubricants are also used by couples during natural intercourse, and it is

important they are assessed for potential effects on sperm cell function and pregnancy outcomes.

Based upon simple motility, the two new lubricants appear to have less deleterious effects on sperm cell function. However, both will need further testing to ensure safety prior to incorporation into the fertility clinic. The Silicone-based lubricant ensures the safety of silicone in the reproductive process, and the Natural lubricant ensures none of its components disrupt the natural hormonal and physiological cascade.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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