Ideal frozen embryo transfer regime

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Purpose of review
This review aims to compare evidence on four criteria (embryo implantation, obstetric outcomes, patient convenience, and IVF-unit efficiency) by analyzing published research on different endometrial preparation methods for frozen embryo transfer (FET).

Recent findings
While the artificial-FET cycle provides advantages in scheduling and implantation, it falls short in ensuring optimal obstetric outcomes. In contrast, natural-FET ensures embryo implantation conditions if ovulation is correctly identified. Supplementing with exogenous progesterone shields against low corpus luteum progesterone secretion, crucial for positive obstetric outcomes. In mNC-FET, ovulation is hCG-triggered, closely resembling natural cycles and reducing monitoring visits for enhanced patient convenience. Letrozole is a recommended option for anovulatory patients, preserving endometrial thickness. It is cost-effective, less likely to induce multifollicular development than gonadotropins, and better tolerated. In a novel approach, the natural-proliferative-phase-FET initiates progesterone in an unmediated ovulatory cycle at 7 mm endometrial thickness, combining the benefits of a natural proliferative endometrium with the convenience of scheduled artificial cycles.

Summary
The artificial cycle offers scheduling advantages, but may compromise obstetric outcomes. Natural FET relies on accurate ovulation timing for successful implantation. mNC-FET simplifies the process using hCG induction, minimizing clinic visits for improved convenience. Letrozole is highlighted as a cost-effective and well tolerated option in anovulatory patients. A recent innovative approach combines elements of natural and artificial cycles, showing promise for FET procedures.

Keywords
frozen embryo transfer, hormone replacement therapy, letrozole, modified natural cycle, natural cycle, obstetric outcome

IDEAL FROZEN EMBRYO TRANSFER REGIME

Introduction

After an unsuccessful fresh embryo transfer cycle or as part of the 'freeze-all' approach, a frozen-thawed embryo transfer (FET) can be performed when there are available frozen embryos. In recent years, the use of FET has surpassed the number of fresh in-vitro fertilization (IVF) cycles [1].During the implantation process, a crucial interaction occurs between the embryo and the endometrium. In physiological conditions, the proliferative phase is characterized by the progressive growth of the functional endometrium in response to rising levels of circulating estrogen. Following ovulation, the secretory phase begins, marked by the secretion of progesterone by the corpus luteum. In simpler terms, progesterone plays a vital role in completing the endometrial preparation after sufficient estrogenic priming.

For FET cycles, endometrial preparation is necessary. Two methods have been developed for this purpose. In the artificial endometrial preparation, also known as the programmed cycle, the goal is to stimulate endometrial growth using estrogens. Subsequently, progestogen is required to create an implantation window, mimicking the natural cycle. There are various types of estrogens, dosages, and administration routes available. Luteal phase support with progestogen can be initiated at different timings. In contrast, natural cycles allow the ovaries

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Curr Opin Obstet Gynecol 2024, 36:000–000

DOI:10.1097/GCO.0000000000000943

KEY POINTS

- The artificial cycle offers scheduling advantages, but may compromise obstetric outcomes.
- Natural FET relies on CL formation combining excellent conditions for embryo implantation, and favorable obstetric outcome.
- hCG is used for triggering ovulation in a time-controlled manner, minimizing clinic visits.
- Letrozole is used to induce mono-follicular development in anovulatory patients.
- Exogenous P is used to supplement the luteal phase.
- Innovative approach combines elements of natural and artificial cycles, showing promise for FET procedures, to be further explored.

to produce estradiol without external stimulation. There are two variants: 'pure' natural cycles, which permit spontaneous ovulation with or without additional luteal support, and 'modified' natural cycles (mNC). The latter involves the use of medication for timed ovulation trigger, with or without additional luteal support through exogenous progesterone or progestins [2].

Nevertheless, there is currently no definitive evidence pointing to the optimal endometrial preparation protocol for maximizing endometrial receptivity. From our perspective, the concept of an 'ideal FET' encompasses four key objectives:

(1) Ensuring the most favorable conditions for successful embryo implantation.
(2) Achieving optimal obstetric outcomes.
(3) Providing maximum convenience for patients.
(4) Enhancing efficiency within the IVF unit.

This review seeks to summarize and compare the available evidence concerning these four criteria based on the findings from published research on various endometrial preparation methods.

The artificial ('programmed') frozen embryo transfer cycle

In recent years, the frequency of FET cycles soared for two main reasons: Significant advance in cryopreservation technology (vitrification), and the increased use of 'freeze all' strategy, mainly for genetic testing and ovarian hyper-stimulation prevention. While in the past the artificial cycle was most commonly used, data in recent years point to the advantage of having a functional corpus luteum in FET cycles. The artificial FET regimen is built on the premise that two hormones are all that is needed for successful embryo implantation: estradiol (E2) to induce endometrial proliferation, and progesterone (P) to induce receptive endometrium. If pregnancy is achieved, both hormones should be administered until the placenta takes over P production. Indeed, this approach secures embryo implantation, but falls short regarding the obstetric and perinatal outcome.

Artificial FET allows for very flexible scheduling, which is an advantage for both the patient and the IVF personnel. Weekend work can be easily eliminated, as well as weekdays workload can be easily balanced.

It is now well established that whenever a functional corpus luteum can be created (either in a natural ovulatory cycle, or with the help of medical intervention), the artificial FET cycle is not recommended [3▪,4▪,5▪]. However, still, we occasionally care for patients who cannot achieve ovulation by any means (mostly menopausal women), and for whom the only way to achieve pregnancy is by the artificial FET cycle.

How to choose artificial FET protocol? Apparently, large meta-analyses fail to identify a 'wining' protocol for hormonal endometrium preparation [2,6].

Artificial FET protocol begins in the 'follicular phase' during which E2 is administered to induce endometrial proliferation. According to physiology, the follicular phase is 7–21 days in duration. However, in artificial FET cycle, E2 exposure duration can be very flexible from only 1 week [7] to even 2 months [8]. Estradiol treatment (either orally or trans-dermal) usually begins on day 2 or 3 of cycle, after confirming ovarian quiescence, and continues for 10–14 days. Endometrial width (>7 mm) and its triple-layer pattern is ascertained, while a leading ovarian follicle is ruled out by conventional ultrasound scan. A blood test is taken to rule out spontaneous ovulation, which may hinder endometrial receptivity scheduling. If E2 treatment starts in the early follicular phase, spontaneous ovulation is rare, and can be totally eliminated with GnRH agonist pretreatment to ensure ovarian quiescence during endometrial proliferation. Luteal phase P starts according to the age in which the embryo was frozen (e.g., 5 days before embryo transfer in case of a blastocyst). P can be administered orally, vaginally, rectally, or by injections (I.M. or S.C.). P treatment can be stopped at luteal placental shift (7 weeks gestational age); however, it commonly continues up to week 12 (by 'clinical routine'). From the patient perspective, a side effect free oral preparation is of advantage, and since the outcome is apparently comparable, this is an important point to consider [9].

In the postmenopausal woman, FET cannot be based on ovulation, therefore artificial FET protocol is the only valid approach. The aging normal uterus does not lose its ability to allow successful implantation, and it is able to carry pregnancy to term apparently without any problems even after 50 years of age. Before attempting the index treatment cycle, a mock cycle is advisable to rule out any intra-uterine abnormality (mostly polyps and submucous myoma), and to ascertain normal endometrial development.

In summary, the artificial FET cycle is of advantage as far as scheduling and embryo implantation are concerned, but falls short in securing best obstetric and perinatal outcomes. In addition, patients need to continue medications for weeks, adds to treatment burden.

Natural cycle frozen embryo transfer

This approach relies on exact and accurate timing of the natural ovulation which dictates FET timing [10▪]. We need to identify the onset of luteinizing hormone (LH) surge, and ovulation that follows. Currently, there is no consensus as to the clinical approach to pinpoint the onset of LH surge, or to precisely define the time interval between the onset of LH surge and ovulation. Moreover, the LH surge does not follow a uniform pattern. Rather, three LH surge patterns were identified: spike, biphasic, and plateau (ref as above). LH surge pattern and amplitude may have an impact on the ability of the resulting corpus luteum to produce enough P required for successful implantation. LH surge pattern may change from cycle to cycle in the same patient, hence the effectiveness of the resulting corpus luteum to sustain implantation and early pregnancy development in a specific ovulatory cycle.

LH surge detection by urinary kits is patient friendly; however, a delay may exist between LH surge timing measured in the serum, or by urinary LH kit. Urinary LH kits may also detect premature LH rise, which is not followed by ovulation. This may lead to erroneous scheduling of FET. An ongoing trial is underway to provide further insights [11].

Repeated ultrasound scans can be used to confirm ovulation by the following signs: disappearance, or sudden decrease in the dominant follicle size, increased echogenicity, irregularity of follicular walls, and appearance of free fluid in the pelvis. Blunted LH surge and/or diminished LH receptor expression by the corpus luteum may give rise to luteinized un-ruptured follicle (LUF). Apparently, whereas blunted LH surge may be sufficient to trigger oocyte meiosis resumption, the mechanical rupture of the luteinized follicle requires higher LH levels. Importantly, a significant inter-cycle variability in luteal phase P production may pose an additional challenge. Therefore, a serum P measurement a day before, or on 'day 5' FET, is suggested to determine whether exogenous P is needed.

How important is it to precisely time ovulation and FET? The answer to that question is directly related to the window of implantation (WOI) duration. Wilcox *et al.* [12] followed 221 women trying to conceive for 6 months. Implantation occurred in a wide range of 6–12 days after ovulation. However, most successful pregnancies were recorded when implantation occurred 8–10 days after ovulation. Late implantation was associated with increased miscarriage rate.

Additional P for all? Given the above-described problematic reliability of a random corpus luteum in terms of adequate P production during the luteal phase, global P supplementation in natural FET cycles can be considered [13▪,14]. Which type and dose of supplemented P? Based on the available research, there is no consensus as to the type, dose, and duration of supplemented P [15▪▪].

Obstetric and perinatal outcome following natural cycle FET: Recent meta-analyses seem to form a consensus as to the advantage of the natural FET vs. the artificial FET for the following endpoints: hypertensive disorders of pregnancy, preeclampsia, postpartum hemorrhage and cesarean section rate, preterm birth, large for gestational age baby [4▪,15▪▪,16].

General clinical recommendations for a natural cycle: FET using cleavage stage embryos ('day 3 embryos') is performed 4 days after LH surge. Blastocyst stage embryos are warmed and transferred 6 days after LH surge. Serum P measurement is recommended a day before FET to confirm adequate P production by the corpus luteum. If P is too low, the cycle can be canceled, or exogenous P used thereafter. A viable approach is to supplement every patient with P; type, dose and duration are left for the clinician to decide.

In summary, natural FET secures embryo implantation conditions if ovulation is correctly identified and timed. Exogenous P may shield against low P secretion by the corpus luteum.

Corpus luteum formation is the key for positive obstetric and perinatal outcome.

Patient burden is a concern, since occasionally multiple visits to the clinic are needed.

Scheduling is limited, since ovulation dictates FET timing.

Modified natural cycle frozen embryo transfer

In mNC, human chorionic gonadotropin (hCG) is used to simulate the LH surge when the dominant

follicle reaches a size of 16–20 mm in diameter, as criteria to trigger ovulation in most randomized clinical trials [17,18]. Furthermore, the addition (if any) of progesterone/progestins for luteal support varies widely, with significant differences in dose, type, and route of administration across different studies. Currently, there is no consensus on the effect of luteal phase progesterone supplementation [19]. As an additional note, while the existence of luteal phase defect remains uncertain [20], providing luteal support might be beneficial for a specific subset of patients characterized by inadequate progesterone production from the corpus luteum in terms of both quantity and duration. Notably, advanced maternal age patients are particularly at risk of reduced corpus luteum activity, as evidenced by lower levels of both progesterone and estrogen within this demographic [21]. Arguably, hCG triggering along with progesterone supplementation might address the potential lack of endogenous LH or a suboptimal corpus luteum. As a result, many fertility clinics use luteal phase progesterone support to enhance implantation rates in FET.

Triggered ovulation for all?

Three retrospective studies, spanning over 5000 cycles, comparing unaltered natural cycles with modified ones, failed to uncover notable differences in clinical outcomes [22–24]. However, a recent extensive retrospective analysis ($n = 2353$ cycles) did demonstrate a significant disparity in pregnancy outcomes favoring pure natural cycle over mNC-FET. Randomized controlled trials (RCTs) also show conflicting results: while Weissman *et al*. [22] did not find any significant differences between spontaneous vs. triggered ovulation cycles [25], Fatemi *et al*. [26] had to halt their study prematurely as an interim analysis showed significantly lower pregnancy rates in women who received hCG [26].

After triggering ovulation, additional P for all?

When the decision to induce ovulation is made, two small retrospective studies have reported higher clinical pregnancy and live birth rates when vaginal progesterone was administered. In contrast, another retrospective study found similar ongoing pregnancy rates, whether or not vaginal progesterone was used [27]. Furthermore, a recent RCT did not demonstrate the superiority of intramuscular progesterone over no treatment in terms of clinical pregnancy rates; however, there was a trend towards a higher clinical pregnancy rate with progesterone supplementation in this study [28].

In the context of mNC-FET, the optimal day for embryo transfer has not been rigorously examined. According to a recent review, the recommended approach involves warming and transferring blastocysts 7 days after hCG trigger [29].

From an obstetrics standpoint, a modified natural cycle closely mirrors the natural cycle, differing only in the use of hCG injection to trigger ovulation instead of relying on the spontaneous LH surge. Consequently, outcomes in modified natural cycles appear to parallel those in pure natural cycles [30].

Considering both patient comfort and IVF unit efficiency, it's worth noting that detecting ovulation in the currently applied pure NC FET regimes demands numerous monitoring visits. On the other hand, employing hCG in the mNC-FET cycle enhances flexibility and simplifies FET scheduling as demonstrated in a recent retrospective study showing comparable clinical outcomes when FET is planned by triggering with rhCG when the dominant follicle size ranges from 13 to 22 mm if adequate endometrial characteristics are met, allowing for a flexibility of 5–7 days [31]. Coordinating embryo transfer in the natural cycle proves to be a complex task. In this context, the mNC-FET approach stands out, requiring significantly fewer visits. This not only translates to cost savings but also offers patients a more convenient and practical choice [31,32]. Patients must be aware of the fact that whenever FET relies on corpus luteum formation, a natural conception may occur, in addition to potential conception by the transferred embryo(s), increasing the risk of multiple pregnancy.

In summary, in mNC-FET, hCG triggers ovulation in the absence of a consensus on progesterone supplementation. From an obstetric perspective, mNC closely resembles natural cycles, with hCG induction simplifying the process. The mNC-FET approach minimizes monitoring visits, enhancing patient convenience and cost-effectiveness, making it a practical choice.

Strategies for anovulatory patients

In polycystic ovary syndrome (PCOS) patients, the NC-FET protocol is infrequently employed due to the prevalent irregular menstruation and oligo-anovulation. Instead, artificial cycles and ovarian stimulation techniques are widely favored in these cases. Recent evidence indicates that using an ovarian stimulation protocol before FET may outperform artificial protocols, resulting in significantly higher live birth rates and reduced risks of miscarriage, preterm birth, and preeclampsia [33].

Stimulation protocols utilize medications such as clomiphene, letrozole, and gonadotropins to simulate natural follicular development, encouraging endogenous estradiol production. Subsequently, hCG is commonly used as a surrogate LH surge, aiding endometrial receptivity. Although the superior

stimulation drug remains undetermined, letrozole induction appears promising for patients with abnormal ovulation, showing a correlation with optimal reproductive outcomes [34,35]. Letrozole, unlike clomiphene, is suitable for endometrial preparation in FETs for anovulatory patients, as it does not thin the endometrial lining. While gonadotropins represent an alternative, letrozole is cost-effective, less likely to

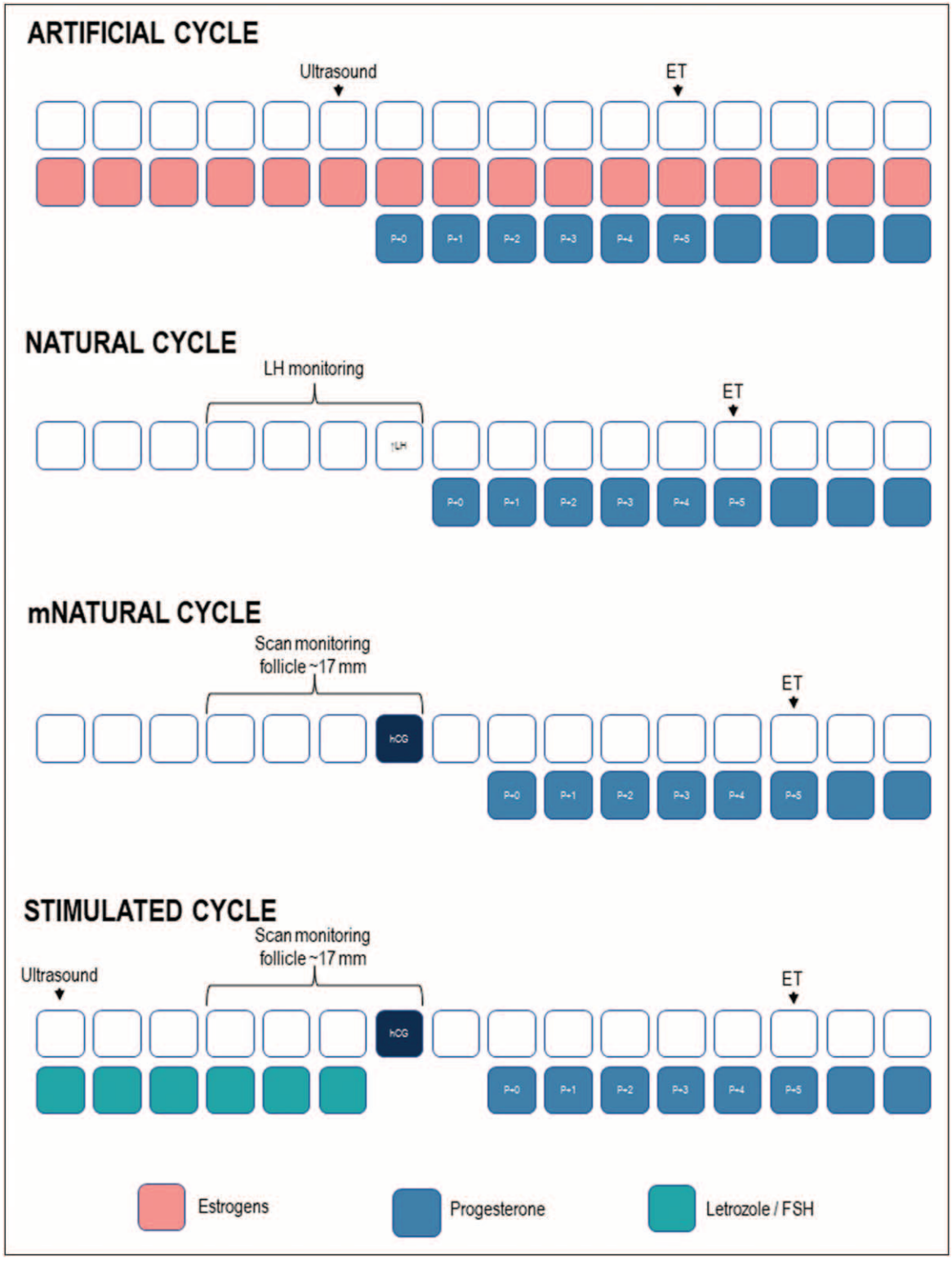

FIGURE 1. Schematic representation illustrating the protocols employed for endometrial preparation in frozen embryo transfer cycles. hCG, human chorionic gonadotropin; LH, luteinizing hormone; P, progesterone. Modified after MayoAlonso *et al.*

Table 1. Advantages and limitations of the protocols for endometrial preparation for frozen embryo transfer

Protocol	Advantages	Limitations
Artificial cycle	Flexible scheduling. Optimal embryo implantation.	Patient burden due to continued medication use. Suboptimal obstetric outcomes.
Natural cycle	Mimics natural conditions. Potential for fewer obstetric complications.	Patient burden with multiple clinic visits. Limited scheduling due to ovulation timing. Possible risk of natural conception.
Modified natural cycle	Enhanced flexibility. Simplified scheduling. Fewer clinic visits.	Uncertain impact of progesterone supplementation. Possible risk of natural conception. Unclear optimal day for embryo transfer.
Stimulated cycle for anovulatory patients	Optimal live birth rates. Reduced miscarriage risks compared with the artificial cycle.	Ovarian stimulation may lead to multifollicular development. Potential for ovarian hyperstimulation syndrome. Choice of stimulation drug not universally determined.

induce multifollicular development or ovarian hyperstimulation syndrome, and better tolerated than injectable medications.

Novel strategies: natural proliferative phase frozen embryo transfers

A recent innovative approach involves initiating progesterone in an unmediated ovulatory cycle once the endometrial thickness reaches 7 mm, irrespective of the dominant follicle's size [36▪]. In a single-center retrospective study ($n = 2158$), the authors report similar ongoing pregnancy rates after 22 weeks, but with less miscarriage rates comparing to artificial cycles (18.4 vs. 30.7%). On the contrary, the comparable serum progesterone and miscarriage rates to NC-FET suggest the possibility of ovulation in the study group, though causality cannot be firmly established due to the retrospective design. This discovery is particularly intriguing given ample evidence demonstrating efficient prevention of ovulatory LH peak in the presence of high progesterone levels [37]. On a positive note, this protocol eliminates the need for exogenous hCG administration or spontaneous LH peak monitoring. It combines the benefits of the natural proliferative endometrium seen in natural cycles with the convenience of scheduled artificial cycles, making it a promising alternative for FET procedures.

CONCLUSION

Recent years have witnessed a global change in IVF practice, where FET cycles increased in number and success rate. Therefore, a search for the ideal FET regimen is of paramount importance. The focus in patient preparation for FET is whether a CL is formed or not. The artificial cycle, devoid of corpus luteum formation, offers scheduling advantages, but may compromise obstetric outcomes. Natural FET relies on accurate ovulation timing for successful implantation, and corpus luteum formation. mNC-FET simplifies using hCG ovulatory trigger, establishing exact ovulation timing, and minimizing clinic visits for improved convenience. Letrozole is highlighted as a cost-effective and well tolerated option in inducing mono-follicular ovulation in anovulatory patients, to be followed with hCG trigger as in the mNC-FET approach. Patients must be aware of the fact that whenever FET relies on corpus luteum formation, a natural conception may occur, increasing the risk of multiple pregnancy (Fig. 1 and Table 1). A recent innovative approach combines elements of natural and artificial cycles, showing promise for FET procedures, to be confirmed in future research, together with the search for the ideal P supplementation.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

None.

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- ▪▪ of outstanding interest

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