

Feasibility of a Progesterone Modified Natural Protocol (P4mNFET) for Frozen Embryo Transfer: A Pilot Cohort Study

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Table of Contents

Original Manuscript.....	5
Supplementary Files.....	21
0.....	22
Figures	23
Figure 0.....	24
Figure 1.....	25
Multimedia Appendixes	26
Multimedia Appendix 0.....	27
Multimedia Appendix 0.....	27
Multimedia Appendix 1.....	27
Multimedia Appendix 2.....	27

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Abstract

Background: With the existence of various frozen embryo transfer (FET) methods currently utilised in the field of assisted reproductive technologies (ART), debate surrounding which of these is superior still remains. The aim of all FET protocols is to prime the endometrium and time embryo transfer during the window of implantation. Current methods include the natural cycle FET (NFET), artificial cycle FET (AFET), ovulation induction (OI) and the modified natural cycle FET (mNFET). Each of these harbours, distinct advantages and disadvantages, namely, surrounding the timing of transfer and flexibility conferred through this process. More recently, a newer approach has been utilised whereby the need to monitor or trigger ovulation is circumvented, with luteal phase support commenced once certain follicle diameter and endometrial thickness criteria are met, but prior to ovulation. However, the research into this protocol has certain important limitations that our study seeks to address.

Objective: To assess the feasibility of a Progesterone Modified Natural Cycle protocol for Frozen Embryo Transfer (P4mNFET). The primary outcome will be the presence of a corpus luteum on ultrasound on the day of embryo transfer. The secondary outcomes will include the number of clinic visits required per patient undergoing the protocol, biochemical pregnancy rate, and clinical pregnancy rate.

Methods: We will conduct a prospective cohort study, recruiting 20 women undertaking FET at the Public Fertility Care of The Royal Women's Hospital in Melbourne, Australia. These women will be matched to a control group who have undergone FET within the preceding 12 months of the study start date.

Results: This project received ethics approval on 17th July 2024, with proposed commencement in September 2024, a duration of completion of 9 months, with aim to complete follow-up and submit study publication in September 2025.

Conclusions: At the conclusion of this preliminary study, the aim would be to progress to a non-inferiority randomised controlled trial to compare P4mNFET to the true NFET (tNFET). Clinical Trial: Registered with ANZCTR and ClinicalTrials.Gov. Awaiting registration numbers. <https://www.anzctr.org.au/>. <https://clinicaltrials.gov/>

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Original Manuscript

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Keywords: frozen embryo transfer, natural cycle, artificial cycle, progesterone modified natural cycle, assisted reproductive technology, corpus luteum

Abstract:

Background: With the existence of various frozen embryo transfer (FET) methods currently utilised in the field of assisted reproductive technologies (ART), debate surrounding which of these is superior still remains. The aim of all FET protocols is to prime the endometrium and time embryo transfer during the window of implantation. Current methods include the true natural cycle FET (tNFET), modified natural cycle FET (mNFET), artificial cycle FET (AFET), and ovulation induction (OI) method. Each of these harbours, distinct advantages and disadvantages, namely, surrounding the timing of transfer and flexibility conferred through this process. More recently, a newer approach has been utilised whereby the need to monitor or trigger ovulation is circumvented, with luteal phase support commenced once certain follicle diameter and endometrial thickness criteria are met, but prior to ovulation. However, the research into this protocol has certain important limitations that our study seeks to address.

Objective: To assess the feasibility of a Progesterone Modified Natural Cycle protocol for Frozen Embryo Transfer (P4mNFET). The primary outcome will be the presence of a corpus luteum on ultrasound on the day of embryo transfer. The secondary outcomes will include the number of clinic visits required per patient undergoing the protocol, biochemical pregnancy rate, and clinical pregnancy rate.

Methods: We will conduct a prospective cohort study, recruiting 20 women undertaking FET at the Public Fertility Care of The Royal Women's Hospital in Melbourne, Australia. These women will be matched to a control group who have undergone the tNFET protocol within the preceding 12 months of the study start date.

Results: This project received ethics approval on 17th July 2024, with proposed commencement in September 2024, a duration of completion of 9 months, with aim to complete follow-up and submit study publication in September 2025.

Conclusions: At the conclusion of this preliminary study, the aim would be to progress to a non-inferiority randomised controlled trial to compare P4mNFET to the tNFET.

Trial registration: Registered with ANZCTR and ClinicalTrials.Gov. ANZCTR number ACTRN12624001144505.



Introduction

Frozen embryo transfer (FET) has been increasingly utilised over recent decades in Europe [1,2] and Australia [2]. With advancements in cryopreservation techniques and increasing use of FET, debate

still exists around the optimal method of endometrial preparation to achieve the best possible pregnancy rates and improve various maternal and neonatal outcomes. The most widely used protocols for endometrial preparation include the Natural cycle FET (NFET), Artificial cycle FET (AFET), and Ovulation Induction (OI) methods [3], with the latter two protocols usually reserved for anovulatory women. Whilst the true NFET (tNFET) relies on monitoring for the surge of endogenous luteinising hormone (LH) and rise in progesterone (P4) as markers of ovulation in order to time progesterone (P4) supplementation start and embryo transfer, the AFET protocol involves exogenous hormone (estrogen (E2), followed by P4) administration to mimic the natural cycle and prime the endometrium. Furthermore, whilst the AFET confers greater flexibility in terms of timing FET precisely, there is evidence to suggest lower overall implantation rates and higher miscarriage from this technique [4]. The literature also suggests there may be a higher rate of obstetric complications for both mother and fetus, including pre-eclampsia [5] and fetal macrosomia [6]. Henceforth, the advantage of the tNFET centres on avoiding excessive exogenous hormone administration and resulting adverse events linked to AFET. However, the inflexibility conferred by the tNFET in terms of the need to closely monitor endometrial thickness, follicle size and hormone levels may require multiple blood tests and 7-day in-vitro fertilisation (IVF) clinic availability. Further, the OI protocol involves the expense and invasiveness of using medication without removing the need for a 7-day service or the need for blood tests. Therefore, a protocol that achieves ovulation and gives a degree of flexibility to the timing of embryo transfer would be highly appealing to both patients and IVF clinics.

To address these challenges, some clinics utilise the modified NFET (mNFET) protocol where exogenous human chorionic gonadotropin (hCG) is administered to trigger ovulation when a dominant follicle of typically 17mm or more is detected, thereby conferring some flexibility in scheduling FET whilst still relying on the woman's natural cycle [7]. Retrospective cohort studies have shown favourable outcomes in both the tNFET and mNFET as compared to the AFET [8].

Notably, two recent randomised controlled trials (RCT) showed similar rates of pregnancy in the mNFET as compared to the true NFET (tNFET), with higher implantation rates in the mNFET cohort [7,9]. However, at least one study has reported better outcomes with tNFET [10] and the most recent Cochrane systematic review on cycle regimens FET did not compare tNFET and mNFET [3].

To further explore the potential flexibility conferred by the mNFET method whilst mitigating the lack of flexibility in scheduling transfer, a prospective case series proof of concept study by Weiss et al. [11] has trialled a novel approach whereby timing the FET to the endogenous LH surge is circumvented. Instead, P4 luteal phase support (LPS) via vaginal pessary is commenced once a mature follicle of >12mm is identified on ultrasound (US) and the lining of the endometrium is sufficiently thick at >7mm, with FET scheduled 2-5 days from this point, depending on the stage of the embryo at the time of cryopreservation. It appears that this P4 modified natural protocol for FET (P4mNFET) provides a simultaneous advantage of both retaining a natural cycle, with authors suggesting ovulation took place regardless, as well as conferring greater flexibility for the scheduling of embryo transfer without compromising clinical pregnancy rate. It should be noted that the authors report a degree of variation in the timing of P4 initiation in relation to the last US without any further blood tests. Importantly, no adverse events were reported from this study of 42 participants. A more recent retrospective cohort study comparing this method to AFET demonstrated comparable outcomes in terms of clinical pregnancy, miscarriage, and live birth rate between the methods [12]. A further single-centre retrospective cohort study reported similar results when comparing outcomes from patients undergoing FET cycles within the natural and artificial protocols, as compared to a P4mNFET protocol [13]. Taken together, P4mNFET may confer greater flexibility to clinicians and patients in timing FET, negating the requirement to await ovulation, with comparable outcomes.

Overall, the present study aims to provide greater flexibility in timing transfer by providing participants with vaginal pessaries of P4 to be used prior to FET and subsequently a) confirming the absence of elevated endogenous P4 on the day of P4 supplementation start and b) confirming the

presence of a corpus luteum on US. It is hypothesised that the potential advantages of this P4mNFET protocol, over triggering and manipulating ovulation, may include the increased flexibility in the timing of commencing P4 without the requirement of a large follicle, the elimination of the importance of pinpointing the exact timing of ovulation, and the potential cost-saving to the patient and clinic as a result of these components. It is anticipated that outcomes of this pilot cohort study may inform the planning and development of a subsequent non-inferiority RCT to further reinforce the utility of such a protocol.

Methods

Study Type

The proposed study will adopt a pilot cohort methodology consisting of 12 weeks of intervention and follow-up monitoring of participants for primary and secondary outcomes. Secondary outcomes will be compared with retrospective data from the tNFET control group.

Participants

The study population will consist of 20 women undertaking FET cycles at the Public Fertility Care of The Royal Women's Hospital (RWH), Melbourne, Australia. The recruitment process will commence at this location, whereby clinicians and nursing teams will be invited to screen the patients they interact with for eligibility for the study. These staff members will be trained on appropriate screening according to the study protocol and will be delegated by the principal investigator (PI). Eligible patients will then be approached by the study recruitment team, team members who are not directly involved in potential participants' clinical care and, therefore, will not have had any clinical interactions with the participant. All patients will be provided with a Patient Informed Consent Form (PICF) (Appendix 1) to ensure they are familiar with the protocol requirements and understand their rights as participants. Additionally, they will be provided with a patient information document

created by the research team (Appendix 2) to assist with patient education surrounding the use of the P4 pessary during the study.

Inclusion criteria consist of women with regular cycles defined as 21-35 days, women under 40 years old at the start of a cycle, and whose body mass index (BMI) ranges from 18 to 35 inclusive.

Exclusion criteria include anovulatory women, women who are over 40 years old at the start of the cycle, and women who have pre-existing contraindications to exogenous progesterone supplementation, such as those with liver disease or thromboembolic disease. Exclusion criteria will also include use of additional luteal phase support (e.g. subcutaneous), women with uterine pathology, including congenital malformations of the female reproductive tract, endometrial polyps, intrauterine adhesions, adenomyosis, and leiomyoma. Regarding the retrospective element of the study, patients for whom inclusion criteria information is lacking will not be included in the study.

The control group will consist of retrospective data from 20 women, matched against inclusion and exclusion criteria, within the Public Fertility Services of the RWH data bank. These controls would have undergone tNFET at the service within the preceding 12 months of the study start date.

All participant data will be stored securely in the database of the RWH RSU, ensuring the security of patients' confidential information. Furthermore, on completion of the study, all patient information will be securely stored within the hospital server with restricted access for minimum 15 years, with custodial responsibilities given to the PI.

Outcome Measures

The primary outcome will be the presence of corpus luteum with a characteristic 'ring of fire' appearance on transabdominal US (TAUS) on the day of embryo transfer.

The secondary outcomes consist of the number of clinic visits required per patient undergoing this protocol, the biochemical pregnancy rate defined as the detection of β hCG in serum or urine [14], and clinical pregnancy rate, defined as the ultrasonographic visualisation of one or more gestational

sacs [14].

Randomisation

This is a pilot prospective cohort study without randomisation.

Intervention: P4mNFET Protocol

Participants will undergo active treatment for 2-8 weeks, with a follow-up period of up to 12 weeks or gestation. For a patient with a 28-day menstrual cycle, on day 10-12 (Fig 1.), a transvaginal (TVUS) will be performed to evaluate for an appropriate endometrial thickness of $\geq 7.0\text{mm}$ and mean follicle diameter of $\geq 14.0\text{mm}$. If these US criteria are met, the patient will undergo blood tests for E2, LH, P4 on the same day: should levels of P4 be under 5nmol/L , exogenous progesterone supplementation via vaginal pessary will then commence on the same day, with FET scheduled 120-125 hours post-P4 administration. P4 pessary, ORIPRO® (Orion Laboratories Pty Ltd T/A Perrigo Australia), at a dose of 200mg twice daily, will be the only form of LPS for P4mNFET patients. Following FET, serum βhCG will be taken 10 days later. If positive, LPS, via P4 pessary at 200mg twice daily will continue to 8 weeks' gestation with a pregnancy scan between 6-7 weeks. If negative, the patient will be advised to cease LPS.

In the instances where P4 levels are greater than 5nmol/L , the patient will be removed from the study.

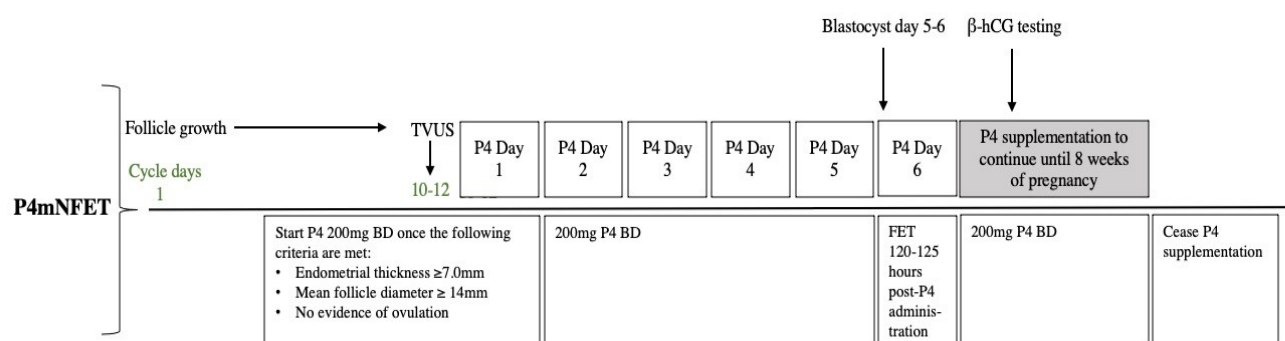


Fig 1. Visual representation of the patient journey with P4mNFET protocol

Control: tNFET Protocol

The control group will consist of patients, matched to the inclusion and exclusion criteria, who would have undergone tNFET at the RWH Reproductive Services Unit (RSU). Patients undertake an US on day 10-12 of their cycle, for those with a 28-day cycle. Upon detection of a dominant follicle of 18mm or more and endometrial thickness of 7mm or more, serum LH and P4 are taken. LH surge is defined as $>25\text{IU/L}$ in the context of $\text{P4} < 5\text{nmol/L}$. Ovulation is defined as a $\text{P4} > 5\text{nmol/L}$. LPS, in the form of vaginal ORIPRO® 200mg pessary (Orion Laboratories Pty Ltd T/A Perrigo Australia), is commenced on day 1 post-ovulation and embryo transfer is carried out 6 days post-LH surge.

Statistical Analysis and Sample Size

Given the qualitative and binary nature of the primary outcome, no statistical testing is proposed for this. Secondary outcomes will undergo t-test and Mann Whitney U testing for data that are normally and not normally distributed, respectively. Should there be significant variation in the key baseline variables between the study and the control group, a multivariate analysis will be performed.

Safety Monitoring and Reporting

Safety oversight for the study will be carried out under the direction of the Independent Safety Monitor (ISM) working within the framework of the Data and Safety Monitoring Board (DSMB) Charter to ensure an objective assessment of safety and efficacy of the study. Adverse events (AE) deemed secondary to the administration of the pessary will be monitored and reported accordingly by either the investigators or the ISM, from administration to the end of follow-up. Relevant physical examinations or investigations will then be carried out to ensure the effects of the AE are managed accordingly. The primary investigator will record the AE appropriately into the patient's medical record or study shadow file.

Integration and Dissemination of Findings

On completion of the study, primary and secondary outcomes will be disseminated to investigators, ensuring confidentiality of patient information. Findings will be synthesised and communicated to colleagues of the RWH RSU and Human Research Ethics Committee (HREC), as well as in further peer-reviewed publications related to the RCT that may be conducted following completion of this cohort study. Additionally, findings will be communicated in a confidential manner at potential presentations in national and international conferences.

Results

Ethical Approval

This project was conceived in November 2023. It was subsequently approved by the RWH HREC on 17th July 2024. Local governance approval was granted on 28th August 2024.

The proposed commencement date for this study is September 2024, with a proposed duration of recruitment of 9 months, between September 2024 and June 2025. The proposed completion of follow-up is September 2025, with anticipated submission for publication at the end of 2025.

Discussion

Overview

We have designed a pilot cohort non-randomised study to assess the feasibility of a novel P4mNFET protocol that circumvents the need to monitor for endogenous LH surge to pinpoint ovulation in order to schedule FET. This protocol, therefore, may combine the advantages of the tNFET, AFET and mNFET into one protocol that provides greater flexibility for the timing of transfer with fewer requirements for surveillance, and no impact on pregnancy outcomes.

Anticipated challenges

As with any study of this kind, some challenges are anticipated with patient recruitment. The research team aim to mitigate this via appropriate counselling and use of our PICF, which is set out in a question-and-answer format.

The second challenge may be the accuracy of the retrospective data for the control group. This is an inherent issue with all retrospective studies. However, it is anticipated that key secondary outcomes will be accurately reported.

Limitations

As with any study, there are limitations to acknowledge. Firstly, cohort studies lack the same level of rigorous methodology as an RCT. However, on the basis of the results of this pilot, we aim to proceed with a non-inferiority RCT to compare this novel protocol to tNFET. Secondly, the retrospective nature of the control group may be associated with issues related to data entry.

Implications

The implications of this study are that it may inform the future of FET. If primary outcomes are met such that presence of the corpus luteum is maintained with P4mNFET, then a non-inferiority RCT will be carried out to formally compare the two methods. Moving forward, this P4mNFET protocol may provide clinics the opportunity to perform FET with greater scheduling flexibility and comparable outcomes to established methods, whilst potentially leading to cost-saving and increased efficiency.

Acknowledgments

Generative artificial intelligence was not utilised in the writing or conceptualisation of this protocol.

This study is supported by The Royal Women's Hospital, Melbourne Victoria.

Funding: nil.

Data Availability Statement

The data sets generated during and/or analysed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

There are no conflicts of interest for the current study.

Authors' Contributions

AC was involved in project conceptualisation, literature search, and writing – original draft. EXG was involved in conceptualisation, writing – review and editing, project administration, and supervision. VA was involved in protocol development and study coordination. AP was involved in study conceptualisation and writing of protocol. WTT was involved in study conceptualisation and writing of protocol.

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Abbreviations

AE/RAE: adverse event/related adverse event

AI: Associate Investigator

ART: Assisted Reproductive Technology

DI: donor insemination

DSMB: Data and Safety Monitoring Board

ET/FET: embryo transfer/frozen embryo transfer

AFET: artificial cycle FET

mNFET: modified natural cycle FET

NFET: natural cycle FET

P4mNFET: progesterone modified natural protocol FET

tNFET: true natural cycle FET

E2: estrogen

hCG/ β hCG: human chorionic gonadotropin/ β -human chorionic gonadotropin

E2: estrogen

HREC: Human Research Ethics Committee

ISM: Independent Safety Monitor

IVF: in-vitro fertilisation

LH: luteinising hormone

LPS: luteal phase support

OI: ovulation Induction

PI: Principal Investigator

P4: progesterone

RCT: randomised controlled trial

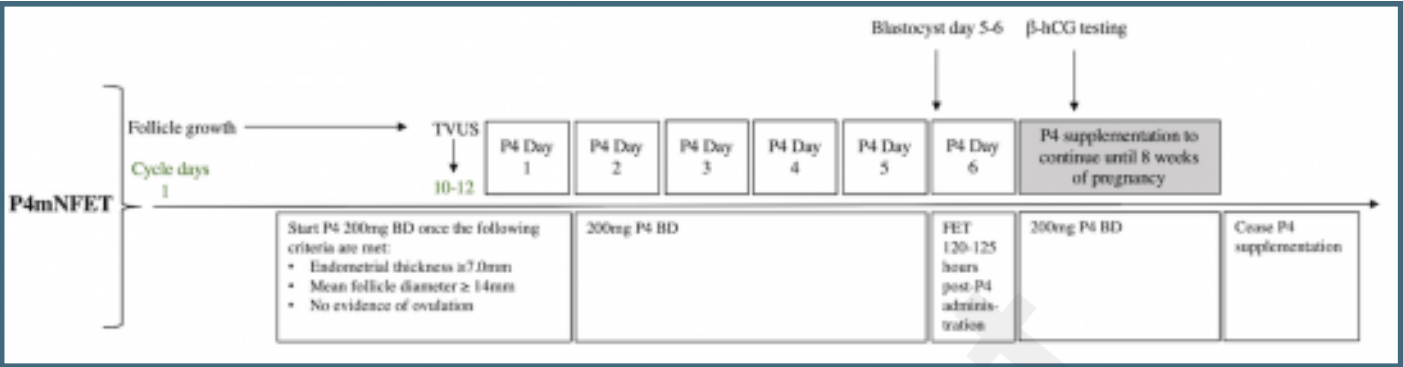
RSU: Reproductive Services Unit, The Royal Women's Hospital

RWH: The Royal Women's Hospital (Melbourne, Victoria)

US/TAUS/TVUS: ultrasound/transabdominal US/transvaginal US

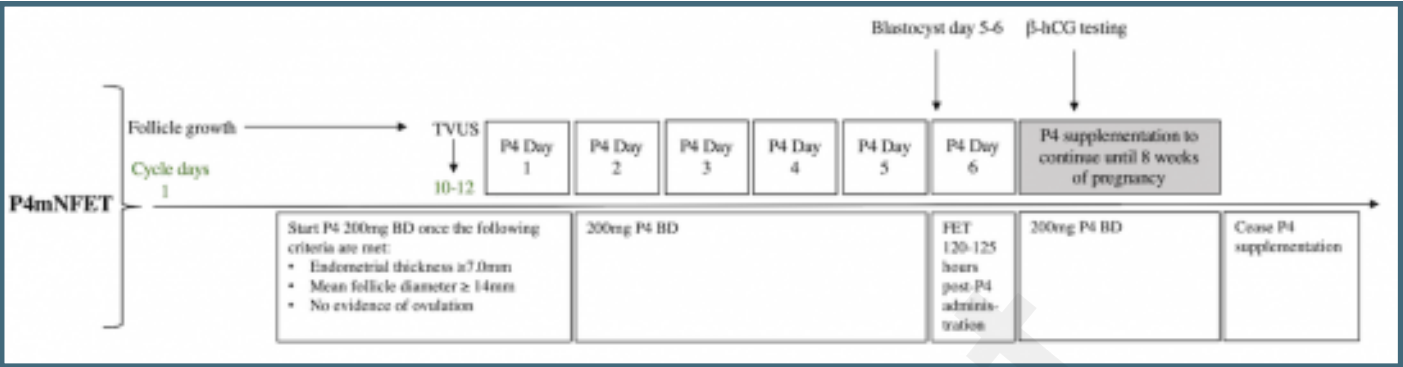
Supplementary Files

Visual representation of the patient journey with P4mNFET protocol.

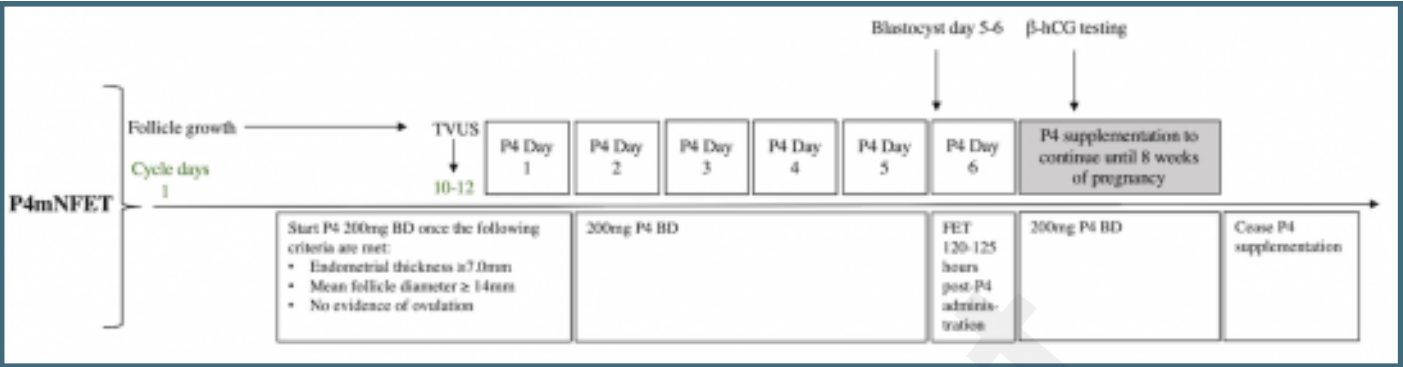


Figures

Visual representation of the patient journey with P4mNFET protocol.



Visual representation of the patient journey with P4mNFET protocol.



Multimedia Appendixes

Patient Informed Consent Form (PICF) for recruitment of patients to undergo the P4mNFET protocol at the Reproductive Services Unit of The Royal Women's Hospital, Melbourne.

URL: <http://asset.jmir.pub/assets/c72141ea473d18f597d70fc2a3bb72ab.pdf>

Participant information sheet for use of progesterone pessary during P4mNFET.

URL: <http://asset.jmir.pub/assets/31711c56d985314b77744c8d4f4e11f6.pdf>

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URL: <http://asset.jmir.pub/assets/649699fc31bdc6a4bdf90c9636d0fd9a.pdf>

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URL: <http://asset.jmir.pub/assets/64c9c6986e348069b729013fe46644e6.pdf>