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RESEARCH

Effects of low-dose oral micronised progesterone on sleep, psychological distress, and breast development in transgender individuals undergoing feminising hormone therapy: a prospective controlled study

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Abstract

Objective: The role of micronised progesterone in hormone regimens for transgender individuals undergoing feminising hormone therapy remains uncertain. We aimed to determine the effect of oral micronised progesterone on sleep quality, psychological distress, and breast development in transgender individuals undergoing feminising hormone therapy.
Design: Prospective case–control study. Twenty-three transgender individuals on stable oestradiol treatment newly commencing 100 mg oral progesterone (n = 23) and controls continuing standard care (n = 19) were assessed over 3 months.
Methods: Pittsburgh Sleep Quality Index (PSQI), Kessler psychological distress scale (K10), and Tanner stage to assess breast development were assessed at 0 and 3 months. Non-parametric analysis of covariance was used to compare differences between groups.
Results: Compared with controls over 3 months, there was no difference in PSQI (P = 0.35), K10 (P = 0.64), or Tanner stage (P = 0.42). There was no significant difference in the proportion of individuals with clinically significant improvement in PSQI (25% vs 22%, P = 0.84). One individual had a significant deterioration in psychological distress that improved following the cessation of progesterone.
Conclusions: Low-dose progesterone was not associated with changes in sleep quality, psychological distress, or breast development over 3 months follow-up, though there was significant inter-individual variability. Larger, placebo-controlled trials are required to further evaluate different doses of progesterone in feminising hormone therapy regimens.

Key Words
- progesterone
- sleep
- transgender
- distress
- breast

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Introduction

Transgender (trans) individuals, including those who are binary and/or non-binary identified, undergoing feminising hormone therapy are often treated with oestradiol with or without anti-androgen therapy. Treatment allows the development of physical characteristics that align with their gender identity and improves mental health (1).

There has been an ongoing debate regarding the inclusion of progesterone in feminising hormone therapy

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regimens. Some suggest progesterone may aid more rapid feminisation with greater testosterone suppression and enhanced breast development (2), however, others raise concerns regarding breast cancer and cardiovascular disease risk with the use of progestins (3). Due to a lack of evidence, progesterone is not currently recommended in expert consensus guidelines (4, 5). Despite this, there are anecdotal reports of improved mood and enhanced breast development amongst trans individuals, particularly on internet discussion forums (4). Medroxyprogesterone acetate, a progestin, has been associated with improved self-reported breast development and greater serum testosterone suppression in a retrospective analysis (6). However, addition of medroxyprogesterone acetate did not enhance breast development in a prospective study (7). There are currently no data with micronised progesterone.

Micronised progesterone is often prescribed for endometrial protection with oestradiol as menopausal hormone therapy for cisgender women with an intact uterus (8). Pre-clinical data demonstrates modulation of the γ-aminobutyric acid type A (GABA-A) receptor, and micronised progesterone treatment has been found to reduce sleep onset latency and to improve self-reported sleep outcomes in randomised-controlled trials enrolling predominantly cisgender post-menopausal women (9, 10, 11). A reduction in anxiety has been reported in a randomised trial of women with pre-menstrual dysphoric disorder (12).

This study was designed to assess the effect of 100 mg oral micronised progesterone (progesterone) on sleep and psychological distress in trans individuals established on feminising hormone therapy for at least 6 months. Secondarily, we aimed to assess the effect of progesterone on breast development. We hypothesised that progesterone would improve sleep quality, reduce psychological distress, and enhance breast development.

Materials and methods

We conducted a prospective 3-month case–control study at Austin Health, a tertiary referral hospital affiliated with The University of Melbourne. Participants were recruited from outpatient clinics from November 2020 to April 2021. Trans adults were eligible for the study if they had been treated with oestradiol for a minimum of 6 months. Exclusion criteria included previous treatment with micronised progesterone, contraindication to micronised progesterone, a history of breast cancer or thromboembolic disease, or severe medical comorbidity. Cases were individuals newly commencing 100 mg oral micronised progesterone and controls were trans individuals continuing standard care oestradiol therapy. Micronised progesterone is frequently requested in clinical care but is not considered routine care in Australia (5). If an individual initiated this discussion, the risks and potential benefits of micronised progesterone were discussed, and if they chose to commence micronised progesterone they were invited to participate in this study. 100 mg oral progesterone is the dose most frequently prescribed in Australia (13). Individuals continuing standard care were invited to participate as controls.

The trial protocol was approved by the Human Research Ethics Committee, Austin Health (HREC/59822/Austin-2020), and each participant provided their written informed consent. The trial was pre-registered with the Australian New Zealand Clinical Trials Registry (identifier ACTRN12620001130954). We followed the STROBE checklist of items that should be included in reports of case-control studies (14).

Assessments occurred at 0 and 3 months. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI), a validated measure of sleep quality (15). The PSQI is comprised of 19 individual items which generate an overall score between 0 and 21 points, where a higher score indicates poorer sleep quality over the past month. A PSQI ≥5 indicates poor sleep quality, while a change of ≥3 is considered clinically significant (16).

Psychological distress was measured using the 10-item Kessler psychological distress scale (K10) (17). Individual items were summed to give a total score between 10 and 50, where a higher score indicates higher psychological distress. We used commonly accepted cut-offs to identify the proportion of individuals who reported high or very high distress (18). A score of 10–15 indicates low psychological distress, 16–21 indicates moderate psychological distress, 22–29 indicates high psychological distress, and 30–50 indicates very high psychological distress. The K10 has demonstrated sound reliability and validity (17).

Breast development was assessed using the self-reported Tanner stage (19). Participants were provided photographs of different Tanner stages to self-select. Serum oestradiol and total testosterone concentration were measured via immunoassays available for routine clinical care in Australia. All laboratories are accredited by the National Association of Testing Authorities.

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Sample size determination

Power calculation was based on the PSQI. Mean PSQI decreased from 10.16 ± 3.60 to 6.27 ± 3.04 over 3 months following initiation of 100 mg micronised progesterone in a study enrolling post-menopausal cisgender women (20). Based on this clinically significant change in PSQI, a sample size of 19 per group was required (power 0.9 and level of significance 0.05) to allow for 30% drop-out.

Statistical analyses

Descriptive statistics at baseline were presented as mean (95% CI), with *P*-values from Mann–Whitney test, and frequency (%), with *P*-values from chi-squared test, for categorical variables. Non-parametric analysis of covariance (ANCOVA) (21) was used to test for the difference in PSQI, K10, and Tanner stage between the progesterone group and the control group, adjusted for the corresponding measure at baseline. Chi-squared tests were used to compare the proportion of participants with clinically significant changes in the PSQI and Tanner stage. The reliable change index was calculated for K10, and the proportion of participants with a clinically significant change determined using the Jacobson-Truax method was compared using Fisher's exact test. A two-tailed significance level of $P < 0.05$ was used. Analyses were performed in R version 4.1.1, and the same package was used for non-parametric ANCOVA (22).

Results

Of 54 individuals invited to participate, 42 were enrolled in the study (Fig. 1). Six individuals reported prior or current treatment with micronised progesterone, three individuals declined to participate, and three did not complete the baseline questionnaires. Of 23 individuals in the micronised

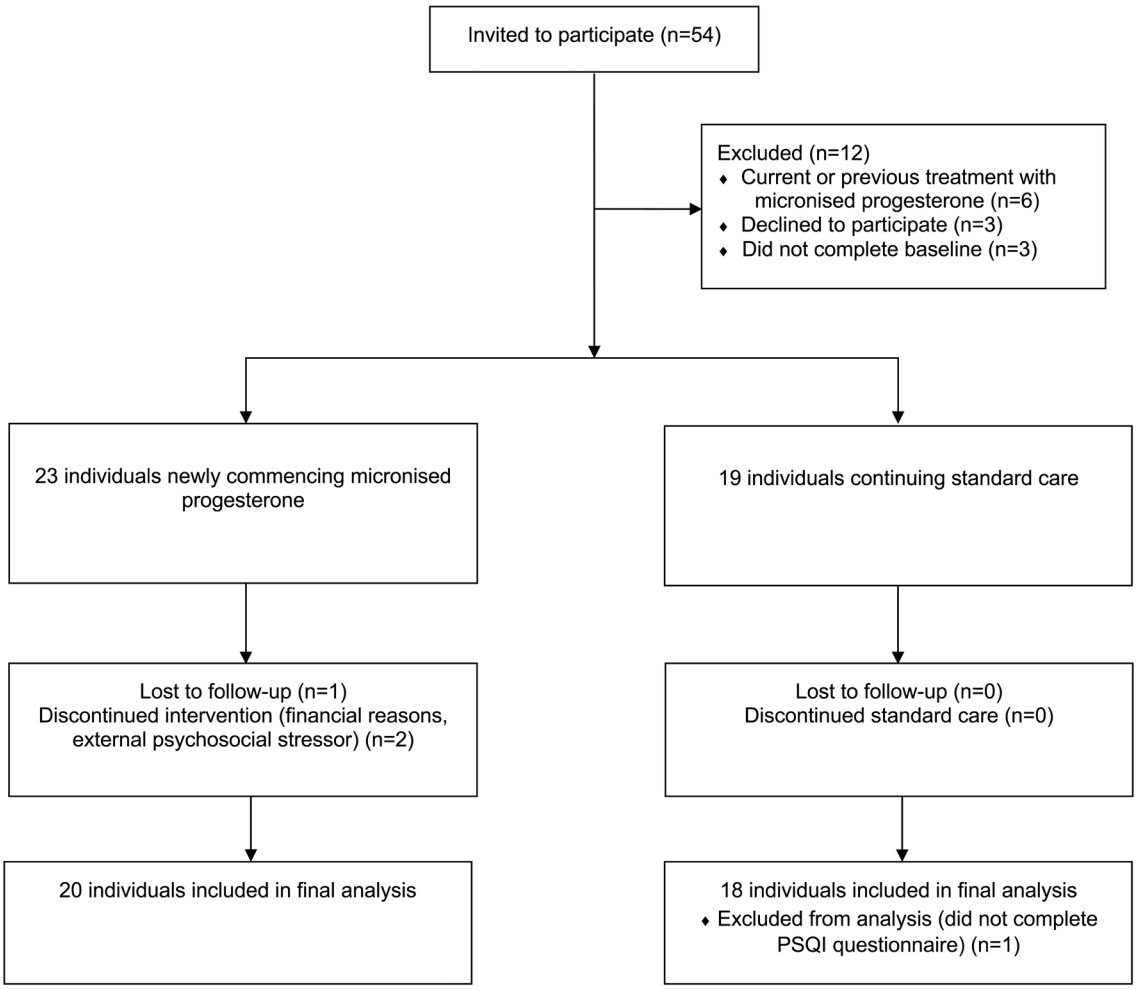


Figure 1
Study subjects and flow of participants.

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Table 1 Baseline characteristics of the study participants. Data presented are mean (95% CI) or number (%). *P*-values <0.05 were considered statistically significant between groups (Mann–Whitney or chi-square for frequencies).

Baseline characteristics	Progesterone group (*n* = 23)	Control group (*n* = 19)	*P*-value
Age (years)	34.9 (29.1, 40.6)	32.1 (25.4, 38.8)	0.4
Duration of feminising hormone therapy (months)	21.6 (15.3, 27.8)	30.3 (14.6, 46.5)	0.9
Dose of oestradiol therapy (mg/day)	3.3 (1.6, 5)	3.0 (1.4, 4.6)	0.7
Oral (mg/day)	5.7 (4.6, 6.8)	4.8 (3.9, 5.7)	0.4
Transdermal patch (µg/24 h)	135 (108, 162)	104 (95, 133)	0.5
Transdermal gel (mg/day)	–	1.5 (1.5, 1.5)	–
Estradiol (pmol/L)	299.6 (215.5, 383.7)	245.7 (168.2, 323.1)	0.4
Total testosterone (nmol/L)	2.1 (0.7, 3.6)	3.4 (0.4, 6.1)	0.6
Orchidectomy	6 (26%)	3 (16%)	0.4
History of depression (*n*, %)	9 (39%)	9 (47%)	0.8
History of anxiety (*n*, %)	9 (39%)	7 (37%)	1
PSQI	7.7 (6.3, 9.2)	8.4 (7.1, 9.8)	0.4
K10	24.4 (21.0, 27.8)	25.2 (22.0, 28.4)	0.7
Tanner stage	3.3 (3.1, 3.6)	3.3 (3.0, 3.7)	0.8

K10, Kessler psychological distress scale; PSQI, Pittsburgh Sleep Quality Index.

progesterone group and 19 individuals in the control group, 3-month PSQI data was available for 20 and 18 individuals, respectively. One individual in the progesterone group was subsequently excluded after a significant external psychosocial stressor, one lost to follow-up, and another temporarily ceased hormone therapy due to financial reasons. One individual in the control group did not complete the entire PSQI questionnaire.

Baseline clinical characteristics are shown in Table 1. There was no difference in age, duration of feminising hormone therapy, sex steroid concentrations, and history of anxiety and/or depression. Baseline PSQI, K10, and Tanner stage are shown in Table 2.

Estradiol therapy consisted of oral (dose range 2–8 mg daily, *n* = 18), transdermal (dose range 50–200 µg/24 h, *n* = 17), 17-β oestradiol gel (dose 1.5 mg daily, *n* = 3), or combination of oral and transdermal therapy (*n* = 4).

Table 2 Within-person 3-month change in those with added low-dose oral micronised progesterone vs controls. Mean (95% CI) are reported. *P*-value from non-parametric ANCOVA adjusted for the corresponding measure at baseline.

Parameter	Progesterone group	Control group	*P*-value
PSQI			
0 months	7.7 (6.3, 9.2)	8.4 (7.1, 9.8)	
3 months	6.9 (5.1, 8.7)	8.0 (6.7, 9.3)	0.35
K10			
0 months	24.4 (21.0, 27.8)	25.2 (22.0, 28.4)	
3 months	22.5 (19.5, 25.5)	23.8 (20.7, 27.0)	0.64
Tanner stage			
0 months	3.3 (3.1, 3.6)	3.3 (3.0, 3.7)	
3 months	3.5 (3.2, 3.7)	3.6 (3.3, 3.9)	0.42

K10, Kessler psychological distress scale; PSQI, Pittsburgh Sleep Quality Index.

Thirty-one individuals were treated with anti-androgen therapy (cyproterone acetate, *n* = 26, spironolactone, *n* = 5) and nine had undergone orchidectomy.

Sleep

Nineteen (86%) individuals in the progesterone group and 17 (94%) individuals in the control group had PSQI ≥5 (poor sleep quality) at baseline. Compared with controls, in individuals receiving progesterone, PSQI was not significantly different over 3 months follow-up (*P* = 0.35) (Table 2). A clinically significant improvement ≥3 in PSQI was reported in 5 (25%) individuals treated with progesterone and 4 (22%) individuals continuing standard care (*P* = 0.84).

Psychological distress

In all, baseline K10 score was 10–15 in 5 individuals, 16–21 in 11 individuals, 22–29 (high psychological distress) in 13 individuals, and 30–50 (very high psychological distress) in 13 individuals. Compared with controls, in individuals receiving progesterone, K10 was not significantly different over 3 months follow-up (*P* = 0.64) (Table 2). Under Jacobson–Truax classification, 4 (17%) participants had deteriorated and 8 (35%) had improved in individuals treated with progesterone, compared to those continuing standard care in which 1 (5%) deteriorated and 4 (21%) improved (*P* = 0.19).

Breast development

Compared with controls, in individuals receiving progesterone, Tanner stage was not significantly different

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over 3 months of follow-up ($P = 0.42$) (Table 2). An increase in Tanner stage was reported in 4 (20%) individuals treated with progesterone, compared to 3 (16%) individuals continuing standard care ($P = 0.73$).

Discussion

In this controlled prospective study of trans individuals on established feminising hormone therapy, we found high baseline levels of sleep impairment and psychological distress, but no significant change with oral progesterone 100 mg over 3 months of follow-up. There was no significant change in breast development, as measured by Tanner stage, compared to standard care.

Comparison to previous literature

Current literature is limited to the evaluation of medroxyprogesterone acetate (MPA) use as there are no data reporting on micronised progesterone in feminising hormone therapy regimens for trans individuals. MPA is a derivative of 17α-hydroxyprogesterone with agonistic activity at the progesterone, androgen, and glucocorticoid receptors (23). A retrospective analysis of 92 trans individuals from the United States reported a significantly lower mean total testosterone concentration in the 39 individuals treated with MPA in addition to oestradiol and spironolactone, compared to the 53 individuals without MPA (2.7 vs 7.4 nmol/L, $P < 0.001$) (6). Twenty-six (67%) and 11 (28%) individuals treated with MPA reported increased breast development, and decreased facial hair, respectively. These self-reported physical changes were offset by 5 (13%) individuals reporting mood swings, which resulted in discontinuation in one individual.

An earlier study in 60 trans individuals undergoing feminising hormone therapy also compared biochemical and clinical parameters between individuals treated with ($n = 15$) or without MPA but did not find differences between groups (7). However, it should be noted there were small patient numbers treated with MPA, variable regimens and duration of feminising hormone therapy, and the regimens prescribed included ethinyl oestradiol or conjugated estrogens, which are no longer recommended (4, 5).

Progesterone and sleep

Progesterone metabolites are positive allosteric modulators of the GABA-A receptor (24, 25) and have been shown to produce similar changes to sleep architecture as benzodiazepines (26). Micronised progesterone treatment has been shown to improve various polysomnography parameters, including sleep onset latency, in a meta-analysis of randomised-controlled trials predominantly enrolling post-menopausal cisgender women (9). Micronised progesterone was prescribed at doses of 200–300 mg but other studies have demonstrated improvement in self-reported sleep outcomes utilising 100 mg micronised progesterone, though concomitant prescription of oestradiol limit conclusions (9). We did not find a between-group difference using 100 mg micronised progesterone and further studies will need to evaluate higher doses.

Sleep in trans individuals

Consistent with previous literature, our findings have highlighted a high prevalence of self-reported sleep disturbance amongst trans individuals. A cross-sectional analysis found a high prevalence of impaired sleep, defined as PSQI ≥5, in 65 (79%) trans individuals treated with feminising hormone therapy (27). Similarly, an interim analysis of baseline data in the Trying to Understand Relationships, Networks, and Neighborhoods among Transgender women of colour cohort study, revealed 29% of individuals viewed their overall sleep as poor ('fairly bad' or 'very bad') as measured by PSQI (28). These results represent a higher prevalence of sleep impairment than that reported in the general population, where a previous cross-sectional analysis of 364 adults from Australia documented impaired sleep in 39.6% of individuals (29).

Importantly, sleep quality has been associated with quality of life, and those with PSQI ≥5 had a significantly lower SF-36 score (75.2 ± 15.0 vs 88.5 ± 6.2, $P < 0.001$) (27). Sleep disturbance was related to an individual's distress, anxiety, and dysphoria related to their gender identity in a qualitative study (30).

Psychological distress

We report high baseline levels of psychological distress and a high prevalence of anxiety and/or depression. This is consistent with a recent survey of 928 trans individuals in Australia in which 73% reported a history of depression and 67% a history of anxiety (31). Previous analyses have utilised the K10 to evaluate psychological distress in trans individuals (32, 33). Forty-six percent of individuals had 'high' or 'very high' levels of psychological distress in an online survey of 169 trans individuals from Australia (33). Similarly, 26 (62%) of individuals in our analysis had 'high' or 'very high' psychological distress at baseline.

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A New Zealand survey reported K10 scores almost two S.D. higher than that of the general population (32). There are currently no longitudinal studies prospectively evaluating changes in K10 following the commencement of hormone therapy.

Although there was no between-group difference in psychological distress, one individual had a significant deterioration in psychological distress following the commencement of oral progesterone. Similarly, two participants reported depression as an adverse effect during a randomised-controlled trial evaluating the efficacy of 300 mg oral progesterone for vasomotor symptoms in post-menopausal cisgender women (34). However, mood adverse effects have not been reported in other trials (12), and depression is reported as a 'very rare' adverse effect in the product information. Nonetheless, this reinforces the importance of monitoring mood after the commencement of oral progesterone.

Breast development

Breast development is a key outcome for many trans individuals. However, the effects of feminising hormone therapy on breast development are often modest (35). Our results are consistent with previous studies that reported Tanner stage, in which most individuals achieved Tanner stage 3 breast development 12–24 months after commencement of feminising hormone therapy (36, 37). Progressive breast development has been reported out to 3 years of follow-up (38) so participants in our analysis may not have achieved maximal breast development. Notably, our 3-month follow-up is likely insufficient to detect potential changes in breast development with micronised progesterone, though changes in Tanner stage are seen within 3-4 months after commencement of feminising hormone therapy (36, 37). Tanner stage is also limited by sensitivity and newer 3D imaging modalities represent alternative methods to quantify the change in breast volume (38).

Limited studies have evaluated the influence of feminising hormone therapy regimens or sex steroid concentrations on breast development in trans individuals. Currently available data have not found a correlation with serum oestradiol concentration (39) but one study has reported a negative correlation between serum testosterone concentration and Tanner stage (37). There are currently no studies evaluating the influence of micronised progesterone on breast development. However as previously noted, 26 (67%) trans individuals reported enhanced breast development with MPA (6). This is discordant with another analysis in which there was no difference in breast development between those treated with or without MPA (7).

Limitations

Limitations include the relatively small sample size and short duration of follow-up. However, our study was powered to detect a clinically significant difference in the primary outcome, sleep quality. While our study was not randomised or blinded, it could be anticipated that self-selected individuals commencing progesterone may have experienced a placebo effect, driving the outcomes in the direction of a progesterone-associated benefit. Although this is speculative, at least we have no reason to suspect that the non-blinded design should have biased our outcome towards missing a progesterone-associated benefit. However, it should be noted that participants had a lower PSQI to that in the study used for sample size calculation, so it may also be that treatment failed to improve PSQI because participants had less impaired sleep quality.

Although progesterone is not recommended in any guidelines for gender-affirming hormone therapy, some practitioners prescribe low-dose oral progesterone (13). It should be noted that high-dose oral progesterone is required to achieve luteal phase progesterone concentrations for 24 h in cisgender women (40). Similarly, randomised trials evaluating the influence of progesterone on sleep parameters using polysomnography used 300 mg at night (9, 10, 11, 41), so higher doses may be required to demonstrate changes in sleep parameters.

Tanner stage lacks sensitivity to quantify changes in breast volume, and the short duration of follow-up may have missed progressive breast development following commencement of micronised progesterone, but this was a secondary outcome. Similarly, we did not have external validation of the self-reported Tanner stage. The optimal dose of micronised progesterone in trans women is not known, and some prescribe this cyclically (13). Although not a primary outcome, serum sex steroid concentrations were measured by immunoassays available in routine clinical care. The influence of micronised progesterone on serum testosterone concentration was not able to be assessed given that serum testosterone concentration was within the cisgender female reference range at baseline.

Nonetheless, this is the first prospective controlled study to evaluate the addition of micronised progesterone to feminising hormone therapy regimens in trans individuals.

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Conclusion

In this controlled prospective study of trans individuals on established feminising hormone therapy, we report high baseline levels of sleep impairment and psychological distress, but no significant change with the addition of low-dose oral progesterone. There was no significant change in breast development compared to standard care. Larger, randomised placebo-controlled trials with higher doses of oral progesterone added to feminising hormone therapy regimens remain necessary.

Declaration of interest

B J N and A S C have received product from Besins Healthcare for other investigator-initiated clinical studies using oestradiol and progesterone. No product was received for this study. No monetary support from Besins Healthcare has been received for any studies and Besins Healthcare have had no input into the design, analysis, or writing of any manuscripts. M G has received research funding from Bayer Healthcare, Otsuka, and speaker's honoraria from Besins Health Care and Novartis.

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