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SEXUAL HEALTH

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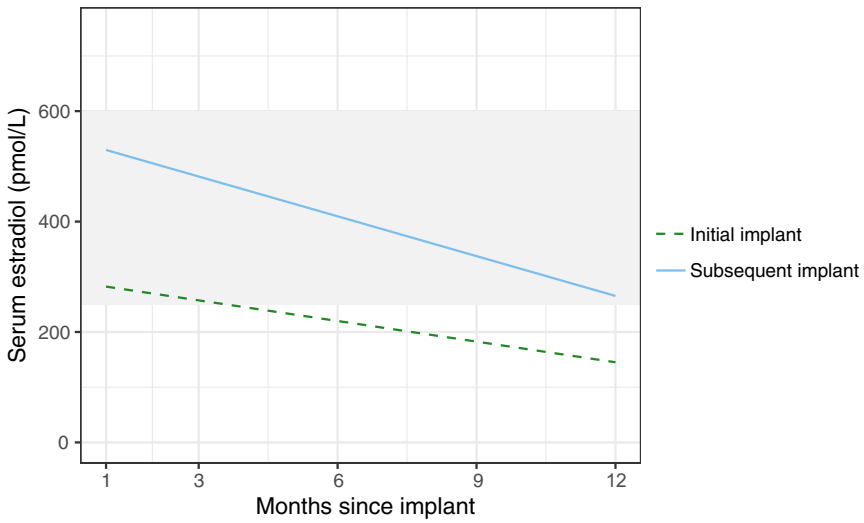
The publisher regrets that Fig. 3 in the published PDF on page 555 was incorrect. The corrected Fig. 3 is shown below.



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SEXUAL HEALTH

Oestradiol implants for gender-affirming hormone therapy: an observational study of serum oestradiol levels and consumer survey

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ABSTRACT

Background. Custom-compounded subcutaneous implants are being used widely in Australia for gender-affirming hormone therapy. However, there is no published literature regarding their use for this purpose. **Methods.** Electronic medical records were audited for consecutive clients who received oestradiol implants April 2019–November 2022 in gender clinics held within Hunter New England Health District in New South Wales, Australia. Serum oestradiol levels were analysed for implant doses 50–200 mg, and predicted oestradiol level was modelled following 100 mg implant insertion. An electronic consumer survey was sent to a convenience sample of implant recipients. **Results.** A total of 38 clients received 88 implants, with 100 mg oestradiol implants being the most frequently used (68%). The median interval between insertion procedures was 270 (IQR 186–399) days. The median serum oestradiol levels following implant insertion, for all implants combined, were within the target range of 250–600 pmol/L at 1-, 3-, 6-, 9- and 12-month time points. Following insertion of a 100 mg implant, the estimated time to reach a predicted serum oestradiol of ≤250 pmol/L was 4 months after an initial implant, and 13 months after subsequent implants. Seventeen consumer surveys were received from 28 invitations. All respondents had previous experience of oral and/or transdermal oestradiol use. Oestradiol implants were preferred due to ease of use, perceived effectiveness, and the belief that other methods were less safe or associated with intolerance and side effects. **Conclusions.** Oestradiol implants are effective in achieving target serum oestradiol levels over a sustained period. Further research with larger cohorts could identify the optimal dosage regimen.

Keywords: compounding, gender affirmation, gender-affirming hormone therapy, gender dysphoria, hormone therapy, oestradiol levels, subcutaneous implants, transgender.

Introduction

Gender-affirming hormone therapy (GAHT) is used to align physical appearance more closely with gender identity in order to reduce distress and improve wellbeing.[1] Long-acting depot testosterone undecanoate, given every 3 months, is the most commonly used form of masculinising GAHT prescribed in Australia.[2] The only available long-acting form of feminising therapy in Australia is subcutaneously implanted oestradiol pellets that are produced by compounding pharmacies. Oestradiol implants are preferred by many patients[1] and are included as an option in Australian Informed Consent Standards of Care for Gender Affirming Hormone Therapy,[3] yet literature is lacking regarding their effectiveness for this purpose. Other oestradiol preparations require more frequent action by the user. The most used preparations are daily oral tablets, transdermal gels, or transdermal patches changed once or twice weekly. European guidelines recommend using a transdermal route of oestradiol administration in all patients over the age of 45 years and those with higher risk for venous thromboembolic (VTE) disease.[4,5] Subcutaneous implants similarly bypass first-pass hepatic metabolism and may provide an alternative to oral

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therapy for those with higher VTE risk. Evaluation of the safety and efficacy of implants would improve the capacity of providers to deliver GAHT.

Literature search

There are numerous studies and reviews describing oestradiol implants, including those of registered proprietary manufacture, in postmenopausal women.[6–18] However, a Medline and Embase search using a combination of medical subject headings and keywords from inception (Medline) and 1996 (Embase) up to July 2023 revealed an absence of published clinical studies evaluating oestradiol levels in transgender patients using oestradiol implants for GAHT, and only one published abstract measuring wellbeing rather than clinical efficacy.[19]

Compounding of implants

At the current time, there are no registered proprietary implants in Australia, and oestradiol implants are obtained from compounding pharmacies. All compounded medicines must meet the quality standards outlined in the Therapeutic Goods Act 1989.[20] Compounding pharmacies are required to comply with Australian guidelines to ensure rigourous manufacturing, sterilisation processes and adherence to quality assurance processes. Oestradiol implants, such as those used by participants in this study, are individually produced and weighed using USP grade 100% oestradiol crystalline powder that is tested to certify its potency. The final product is sterilised either by gamma irradiation at a Therapeutic Goods Administration (TGA) approved facility or by a validated process using a biological indicator in an autoclave. Pharmacies compound implants as 50 mg or 100 mg pellets; pharmacies may complete stability studies.

Hunter New England Health gender clinics

Implants were introduced as standard care in Hunter New England (HNE) Health gender clinics in 2019. Doses used are 50 mg, 100 mg, 150 mg or 200 mg, with doses of 150 mg and above requiring insertion of two pellets. Implants are inserted subcutaneously, usually in the buttock. The procedure involves infiltration of the area with local anaesthetic, a small incision (5 mm) with scalpel, and the implant/s introduced through a trocar.[21] Skin closure is achieved with adhesive wound closure strips, and a waterproof dressing applied. Instructional videos are available on the TransHub website.[22] Standard practice in HNE gender clinics is to measure serum oestradiol levels at 1 month and 3 months post-implant insertion, then 3-monthly thereafter. The target range for serum oestradiol levels according to local protocols was 250–600 pmol/L, with levels of up to 1000 pmol/L being considered physiological. Oestradiol levels above 1000 pmol/L are not desired due to the potential risks of nausea, fluid retention and increase in VTE risk.[23,24]

Aims

The aims of this research were: to describe the acceptability, safety and efficacy of oestradiol implants based on the measurement of serum oestradiol levels in transfeminine people receiving GAHT. Ethics approval for this study was granted by the HNE Human Research Ethics Committee (2022/ETH00055).

Material and methods

Audit of electronic medical records

Electronic medical records (EMR) were audited for a cohort of consecutive clients who received oestradiol implants of doses 50–200 mg as standard care in HNE between April 2019 and November 2022. EMR included records for the community health centre clinic where implant insertion was performed, and the district wide EMR for hospital presentations, clinic records, biochemistry results, and correspondence. Data collected included age, body mass index (BMI), implant dose, and results of serum oestradiol levels measured following implant insertion. Any adverse effects reported and documented in the EMR were listed. Any hospital presentations following implant insertion documented in the district wide EMR were recorded and reviewed by two physician authors to assess if related to oestradiol implant.

The STROBE checklist for observational studies was used to review the reporting of appropriate information for an observational cohort study.[25]

Hunter Medical Research Institute provided statistical analysis using Statistical software *R ver. 4.2.2*.[26] The demographic characteristics of participants are shown, with age and BMI reported as medians and interquartile ranges (IQRs). The oestradiol implant therapy was described including number of implants per person; implant dose, stratified by whether this was an initial or subsequent implant: and interval between implants as median (IQR) days. Observed serum median (IQR) oestradiol levels at 1-, 3-, 6-, 9-, and 12-months were based on any measurement that fell within a 2-month period around the timepoint. For example, the median reported for the 1-month timepoint was the median for measurements taken from 0 days to 61 days.

The trajectories of oestradiol level over time after implant insertion were plotted according to implant dose and the initial or subsequent status of the implant. Serum oestradiol levels were compared with local protocol, national and internationally accepted standards with an oestradiol level of 250–600 pmol/L being considered within target, and up to 1000 pmol/L as physiological.[3,23,24]

The estimates of serum oestradiol levels over time after implant insertion were modelled for all 100 mg implants, as the most frequently used dose; independent variables were initial or subsequent implant, time since implant and their two-way interaction. A three-level linear mixed-effects model

was fit, with a random intercept for each participant and each implant nested within participants. The predicted marginal means for all implants, initial implants, and subsequent implants, were predicted at 1-, 3-, 6-, 9-, and 12-months post-implant, along with the predicted differences between initial and subsequent implants and their 95% confidence intervals. The number of months until the predicted oestradiol level was at or below the lower limit of the target range (250 pmol/L) was estimated.

Consumer survey

An anonymised semi-structured qualitative survey was developed by the authors and with external review by two independent reviewers. An electronic survey link was sent to a convenience sample of all participants that had consented to email contact and had received an oestradiol implant during the study period. Survey data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at HNE Health. REDCap is a secure, web-based software platform designed to support data capture for research studies.[27,28] The previous type of oestrogen and route of administration were recorded; a Likert rating was used to establish the participant preferences. Free text questions were used to explore participant choice. Two authors (JM, SF) reviewed all responses and used thematic analysis to identify common themes.

Results

Demographics

A total of 38 participants received 88 oestradiol implants in HNE gender clinics from 11 April 2019 to 10 November 2022. At the time of the first implant insertion procedure, the median age of participants was 28 years; a significant proportion were overweight or obese; eight had previously undergone orchidectomy (Table 1).

Sixteen clients received their first ever (initial) implant in this service. The remaining 22 clients had received implant/s previously with a different provider, making their first implant in this service a 'subsequent' implant.

Implant doses used were 50 mg, 100 mg, 150 mg and 200 mg, with 100 mg being most frequent ($n = 60$, 68.2% of all procedures). Over the follow-up period, physicians were less likely to insert oestradiol implant doses of 50 mg, and no participants received a dose of 50 mg at their third, fourth or fifth procedure. Conversely, higher doses were more commonly used for subsequent procedures, with physicians more likely to use a dose of 200 mg as a subsequent implant.

By the end of the study, 31 of the 38 participants had received two or more implants, allowing analysis of the time between insertion procedures (Table 2). The median time from the insertion of one implant to the next was 270 (IQR 186–399) days. Time between the insertion of an initial implant and the next was shorter at 238 (IQR 168–322) days.

Table 1. Age, body mass index and orchidectomy status of participants at the time of their first implant.

		n (%)
Age (years)	Median (IQR)	27.8 (24.4–38.7)
	<25	14 (37)
	25–44	15 (39)
	≥45	9 (24)
Body mass index category	Median (IQR)	26.9 (23.1–30.5)
	Healthy/underweight	15 (39)
	Overweight	12 (32)
	Obese	9 (24)
	Unknown	2 (5)
Previous orchidectomy		8 (21)

Table 2. Implant number, dose, and time interval between insertion procedures.

		n (%)
Total number of implants per participant	1	7 (18)
	2	16 (42)
	3	12 (32)
	4	2 (5)
	5	1 (3)
Implant dose, across all insertion procedures ($n = 88$)	50 mg	6 (7)
	100 mg	60 (68)
	150 mg	14 (16)
	200 mg	8 (9)
Initial implant dose	100 mg	14 (88)
	Other dose	2 (12)
First recorded implant, not initial implant	100 mg	17 (77)
	Other dose	5 (23)
Days between two implants, all implants	Median (IQR)	270 (186–399)
Days between first two implants, initial implant	Median (IQR)	238 (168–322)
Days between first two implants, not initial implant	Median (IQR)	262 (175–424)
Days between insertion of implants after dose:		
50 g ($n = 6$)	Median (IQR)	322 (287–602)
100 g ($n = 60$)	Median (IQR)	246 (175–385)
150 g ($n = 14$)	Median (IQR)	238 (203–259)
200 g ($n = 8$)	Median (IQR)	301 (272.5–350)

Observed oestradiol levels after 50 mg, 100 mg, 150 mg or 200 mg oestradiol implant

The change in serum oestradiol levels after insertion of the 88 oestradiol implants with follow-up oestradiol levels are shown by implant dose (Fig. 1), and whether the implant was an initial or subsequent implant (Fig. 2). There was

variation in when oestradiol levels were measured and there was significant observed inter-individual variation with the same dose of implant. Most oestradiol levels were below 250 pmol/L after a 50 mg implant (Fig. 1), although there were few implants at this dose. Similarly, the oestradiol level was below 250 pmol/L at most time points following an initial implant (Fig. 2). For 100 mg implants, the observed median serum oestradiol level was in the target range of 250–600 pmol/L at the 1-, 3-, 6-, 9-, and 12-month time points for all implants combined, and in the target range at all time points for subsequent implants, but not for initial implants (Table 3).

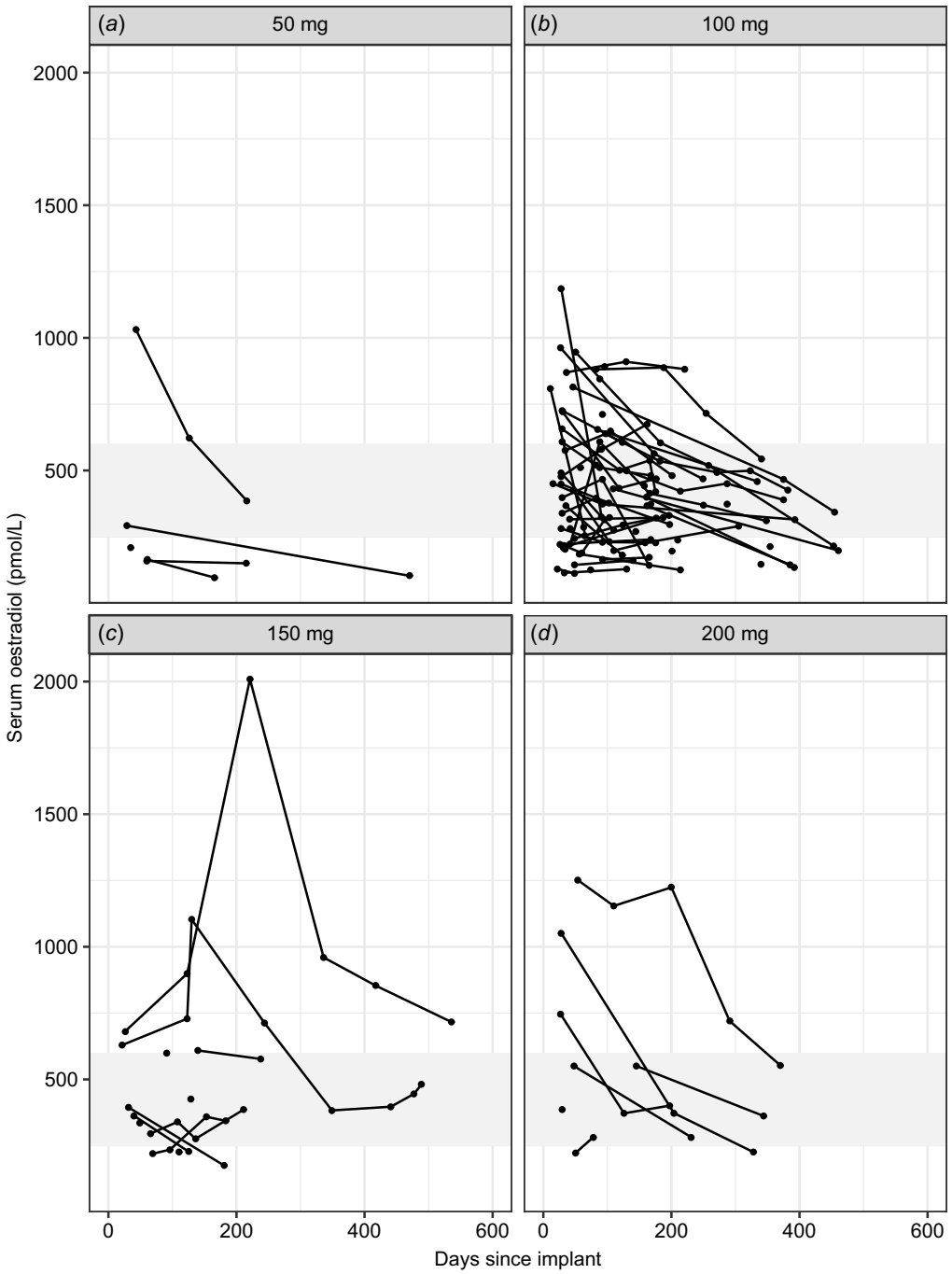

Fig. 1. Observed serum oestradiol levels following implant insertion, by implant dose (*a*) 50 mg $n = 6$, (*b*) 100 mg $n = 60$, (*c*) 150 mg $n = 14$, (*d*) 200 mg $n = 8$. The oestradiol target range of 250–600 pmol/L is shown as a grey bar.

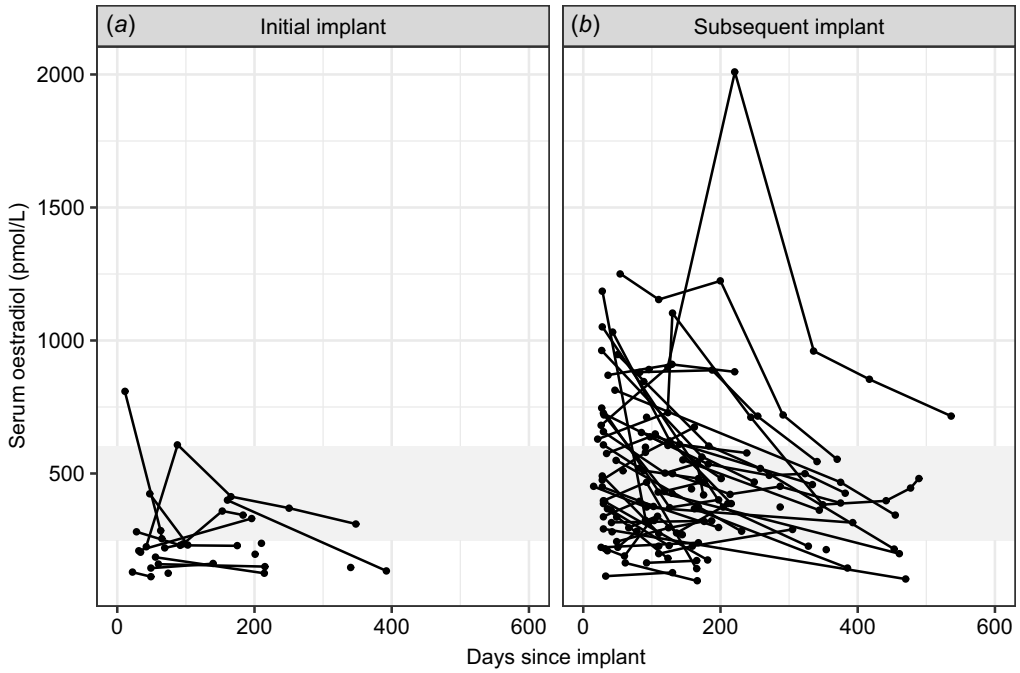

Fig. 2. Serum oestradiol levels following (*a*) initial $n = 16$ and (*b*) subsequent implants $n = 72$. The oestradiol target range of 250–600 pmol/L is shown as a grey bar.

Table 3. Predicted and observed serum oestradiol over time following insertion of 100 mg oestradiol implants ($n = 56$).

	All implants	Initial	Subsequent
Predicted decrease/ month (pmol/L)	−18.2	−12.5	−24.0
Predicted months to 250 pmol/L	10	4	13
Predicted serum oestradiol (pmol/L) post-implant (95% CI)			
1 month	406 (333, 479)	282 (165, 400)	530 (454, 606)
3 months	369 (303, 436)	257 (154, 361)	482 (411, 553)
6 months	315 (248, 381)	220 (116, 324)	410 (339, 480)
9 months	260 (181, 339)	183 (53, 312)	337 (259, 416)
12 months	205 (106, 304)	145 (−24, 314)	265 (172, 359)
Observed median serum oestradiol (pmol/L) post-implant (IQR)			
1 month	397 (220, 632)	207 (154, 267)	476 (316, 721)
3 months	431 (286, 608)	242 (230, 278)	467 (349, 643)
6 months	386 (254, 481)	284 (230, 382)	430 (314, 536)
9 months	468 (412, 506)	Insufficient data	480 (455, 512)
12 months	312 (164, 417)	147 (140, 228)	389 (264, 446)

Observed median serum oestradiol includes tests during the preceding month and following month. Insufficient data means fewer than three tests were conducted.

Predicted oestradiol levels after 100 mg oestradiol implant

The observed oestradiol levels do not account for the longitudinal nature of the data and the repeated measures, therefore predicted oestradiol levels over time were modelled for 100 mg oestradiol implants. The predicted average serum oestradiol level was within the target oestradiol range 250–600 pmol/L for all time points to 12 months for subsequent implants; but for initial implants the predicted level was below the target range from 4 months onwards (Fig. 3, Table 3). Although, the decline in oestradiol levels was slightly slower for initial implants than subsequent implants (12.5 pmol/L/month vs 24.0 pmol/L/month), the predicted number of months to oestradiol equal to or below 250 pmol/L was 4 months for initial implants, but 13 months for subsequent implants (Fig. 3, Table 3).

Adverse events

Most participants had no adverse events related to implant insertion. However, one participant reported insertion site pain that resolved without treatment; one participant experienced vasovagal syncope treated with positioning and without the need for further treatment; and one pellet was fragmented when removed from sterile packaging but was inserted without incident. Recorded hospital presentations were not considered to be related to oestradiol implant insertion; these were admission for surgical draining of infection following unrelated surgery, palpitations following initiation of anti-anxiety medication and oral trauma.

Results of consumer survey

There were 17 survey respondents from 28 invitations to participate. All respondents had used other forms of oestradiol

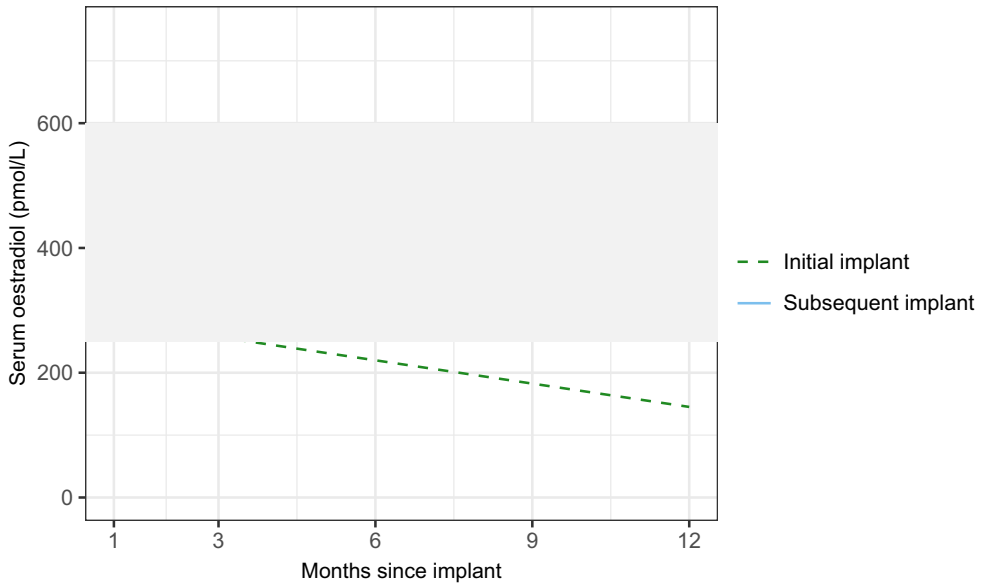

Fig. 3. Predicted average serum oestradiol from 1 month to 12 months post-implant (100 mg oestradiol) for initial and subsequent implants.

previously (Table 4). They were highly likely to continue with oestradiol implants as their method of choice (Likert score 9.5 (s.d. 0.8)/10 – strongly positive), whereas they were less likely to use oestradiol tablets (Likert score 5.4 (s.d. 2.3)/10 – neutral), oestradiol patches (Likert score 3.4 (s.d. 1.9)/10 – negative) or oestradiol gel (Likert score 3.1 (s.d. 1.9)/10 – negative).

The participants cited the following reasons for using oestradiol implants in order of frequency: efficacy, compliance and ease of use, safety, cost, and physician recommendation. The perceived efficacy of implants was represented by comments such as 'when I began implants, I felt much better and my overall results in my body and breast tissue increased tenfold', and ...I was 'able to maintain levels, long term, for less effort.' Many comments related to the ease of use: 'set and forget' compared to challenges of daily, twice weekly, or weekly regimens with other routes of administration; for example, 'I don't have to worry if I miss a day and have a 'panic attack'.' Several participants felt that implants were safer or more cost-efficient, although one participant reported the initial cost of the implant as a barrier to access. Implants may be associated with a reduction of dysphoria: a respondent wrote that ... having an implant 'gives you a feeling of normality' and another that implants 'helped with dysphoria, as taking tablets reminded me daily'. Six participants had negative comments about implants regarding the difficulty in finding a provider, the need to expose the buttock area at the time of the procedure, discomfort from the local anaesthetic delivery and the potential for scarring at the site.

Oestradiol tablets were considered 'simple and cheap' and easily titratable, although some participants considered them ineffective or disliked the 'large number of pills.' There were few positive comments about oestradiol patches, other than the low cost. Oestradiol patches and gels were considered inconvenient, for example 'patches either fell off, left residue on my skin and clothes, or irritated my skin' and gels were found 'annoying waiting for it to dry'.

Table 4. Survey results: previous use of other forms of oestradiol.

	N (%)
Oral oestradiol (pills)	13 (76.5%)
Transdermal oestradiol patch	10 (58.8%)
Transdermal oestradiol gel	6 (35.3%)
Previous use of one form of oestradiol prior to implant	8 (47.1%)
Previous use of two forms of oestradiol prior to implant	6 (35.3%)
Previous use of three other forms of oestradiol prior to implant	3 (17.6%)

Discussion

This is the first demonstration of the acceptability, safety, and efficacy of oestradiol implants for GAHT. This study presents the observed serum oestradiol levels after oestradiol implant insertion, with modelling of the predicted oestradiol levels after a 100 mg dose. We demonstrate that oestradiol implants are convenient for the consumer, have few adverse effects, and provide therapeutic levels of oestradiol up to 12 months, particularly for subsequent implants. A dose of 50 mg was not used commonly as the authors established that for most participants this did not achieve therapeutic levels. There

were few instances of high oestradiol levels, and although these may have been more common with the 150 mg and 200 mg oestradiol implants, this occurred too infrequently for analysis to be feasible. Adverse events were uncommon.

The predicted oestradiol levels following a 100 mg oestradiol implant suggest that there may be a shorter window of efficacy after the initial implant compared with the duration of effect following a subsequent implant. This might suggest that clinicians should counsel their patient that they are likely to need a second insertion within a shorter time frame of approximately 4 months, but that the subsequent implants are likely to last longer. A similar approach is used widely with depot testosterone undecanoate injections, which are generally commenced with an interval of 6 weeks between the first two depot injections, followed by an interval of 10–14 weeks thereafter. Alternatively, a protocol with a higher initial implant dose could be studied, with a review of the serum oestradiol peak and duration.

A recent abstract for a poster presented at Society for Endocrinology BES 2021[19] reviewed self-reported wellbeing and sex-drive of 83 women receiving a 100 mg implant as part of GAHT. Energy, drive, and libido were significantly higher following implant insertion compared to baseline and when compared to other oestrogen delivery methods. This conference reported the average interval between implants was 400 days, and although longer than our median interval of 270 days, the authors note that their oestrogen level had returned to baseline prior to the next implant.

A similar survey with self-reported scoring was undertaken in this study. Responses from our consumer survey demonstrate a strong demand for oestradiol implants among current implant users. All respondents had tried at least one other method prior to oestradiol implants, and many encountered adverse events. Respondents preferred implants for their perceived ease of use, safety, and efficacy. Importantly, several respondents referred specifically to implants reducing their dysphoria, which is arguably the main objective of feminising hormone therapy.

The use of oestradiol implants in GAHT is a new area of research. However, hormone replacement therapy for post-menopausal women is well researched and supported by the evidence of several large randomised controlled trials. According to the 2022 Hormone Therapy Position Statement of the North American Menopause Society, transdermal routes of administration may decrease risk of venous thromboembolism and stroke.[29] Longer-term studies are required to demonstrate if subcutaneous oestradiol implants have a similar safety profile by avoiding first-pass metabolism.[30]

A limitation of this research is that it is a retrospective study of a relatively small cohort of patients within a single gender service. The consumer survey was designed to gather the experience of current implant users, rather than providing comparison with patients not using oestradiol implant therapy. The audit of EMR collected data from all consecutive patients, and includes both initial and subsequent procedures. The implant doses in the study were not randomised but were selected by the clinician based on their expertise and the participants' clinical data. Similarly, the interval between implant procedures was not standardised, but was influenced by clinical factors such as the participants' serum oestradiol levels, as well as other external drivers including appointment availability and time taken to procure the pellets. Given that this is a real-world study, the timing of monitoring was variable, and often less frequent than recommended; however, the experience and outcomes derived from standard care are highly relevant to clinical practice.

Conclusion

Oestradiol implants are safe and effective in attaining therapeutic serum oestradiol levels when used as feminising GAHT. Further collaborative research is recommended to share data across Australia. Research should optimise initial and subsequent implant dose, explore the duration of effect, and consider factors such as body habitus on serum oestradiol levels obtained using implants. Evidence for the safety and efficacy of implants would be important considerations for proprietary TGA approved and Pharmaceutical Benefits Scheme listed products for clients that desire a long-acting oestradiol therapy.

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Data availability. The data that support this study will be shared upon reasonable request to the corresponding author.

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