Observational cohort study exploring MediEmo smartphone app use, live birth and IVF treatment return rates.

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Running title: MediEmo, live birth and treatment return rate

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Capsule: MediEmo use was associated with more live births and treatment returns than non-use suggesting benefits to patients and clinics but replication in a randomised controlled trial is needed.

Abstract

Objective: To explore the associations between the use of the MediEmo smartphone application and IVF live birth and treatment return rates.

Design: A three-year observational cohort study

Subjects: Patients undergoing IVF were classified as users if they used the medication or emotion features of the MediEmo. Patients who did not use the two key features or declined to use the app were classified as non-users.

Exposure: The use of the MediEmo smartphone application.

Main outcome measures: Outcomes of interest were rate of live birth per fresh index cycle, live birth per complete cycle and treatment return for a stimulated cycle of treatment within 12 months of the unsuccessful stimulated index cycle.

Results: A total 1081 patients were eligible to use MediEmo app, 863 were categorised as users and 218 as non-users. MediEmo use was associated with a higher live birth rate per index cycle compared to non-users (27.81% [n=240/863] vs 19.26% [n=42/218], respectively, OR=1.248 95% CI: 1.041, 1.509) and treatment return rate compared to non-users (46.00% [n=169/363] vs 31.37% [n=32/102] respectively, OR=1.339 95% CI: 1.092, 1.656). It was not associated with live birth rate per complete cycle.

Conclusion: The observed positive association between MediEmo use and live birth and treatment return rates suggests benefits to patients and clinics. Further research and replication using a randomised controlled trial design is warranted as is investment in development of digital tools for use during IVF treatment.

Key words: MediEmo use, treatment return rate, live birth rate,

Introduction

Digital tools such as smartphone apps are increasingly used alongside medical treatments. Numerous mobile applications have been developed for IVF settings, but most provide practical, lifestyle or administrative support only, and few are supported by research evidence (1-3).

The MediEmo smartphone app was designed to provide remote practical and emotional management during fertility treatment (4), but also to be applicable for use during any medical treatment that includes both a complex medication regime and medical waiting periods, e.g., waiting for pregnancy test. Features of the MediEmo include a medication timeline that automatically sends notifications to the patient to prompt medication administration according to the patients' medical regime, a mood management component that enables (and prompts) daily emotional monitoring using items from the daily record keeping (DRK) form validated in IVF(5) and evidence based coping tools (6, 7). The app also incorporates information support (e.g., frequently asked questions, symptom checker) that patients can access at any time (see MediEmo features Table 2 in Robertson et al., 2022, (8)).

Initial development, implementation and feasibility data has shown the acceptability and feasibility of implementing the MediEmo in fertility clinics (8). Results from this research demonstrate patients to have high engagement with, and positive perceptions towards, the app particularly the medication timeline. Further, emotional data (i.e., negative and positive emotion scores) collected by the app showed high internal reliability and replicated previous research that shows a pattern of emotional responses (i.e., emotional signature of IVF) experienced during fertility treatment, including the imminence effect of intensified negative emotions as the pregnancy test approached (e.g., (5, 9).

Reliable digital tools, resources or interventions have been suggested to have the capability to change assisted reproduction, patient experiences of treatment and treatment success rates (3). Given the psychological burden of fertility treatment contributes to treatment postponement and discontinuation (10-12), the use of digital tools such as the MediEmo, that provide patient level support through the incorporation of evidence-based resources, in addition to practical and administrative support, could help advance these suggestions further. Moreover, exploring the use of such tools could advance research into the associations between use, treatment continuation and treatment outcomes (e.g., live birth rates).

The aim of the present observational cohort study was to capture real-world data on the uptake and use of MediEmo to prospectively estimate the association between app use (users versus non-users) and the clinical outcomes of live birth and treatments return rates. Based on previous research, we hypothesised a positive association between app use and clinical

outcomes, namely higher return, and live birth rates in MediEmo users compared to non-users.

Materials and methods

The MediEmo study procedures have been described previously (8) but are summarised here. Reporting was according to STROBE checklist for cohort studies.

Participants

Data was collected during the implementation of the MediEmo at a single centre from May 2017 (when MediEmo was introduced in clinic) to September 2020. MediEmo was made available to patients undertaking cycle types with medication regimes suitable for input into the medication management component of the MediEmo app, e.g. medicated FET and stimulated IUI. However, for this study only patients undertaking IVF/ICSI cycles with a plan for fresh embryo transfer were included. Patients undertaking egg sharing cycles (n=8) were excluded. All participants were asked to give their consent for their data to be used in the current non-contact medical research. Ethical approval for this study for the collection and analysis of implementation data was obtained from the University of Southampton and NHS HRA (IRAS 290597).

Materials

MediEmo smartphone application

As reported previously (see Table 2, in Robertson et al., 2022 (8), MediEmo comprises three core components (six features) namely medication management (timeline and messaging), mood management (mood tracking, coping support) and information support (FAQs and symptom checker). All data inputted into the MediEmo is held securely in an, encrypted, cloud-based portal (see full development details and Supplementary Materials and Methods(8).

Measures

1. *MediEmo Usage*

Patients were assigned to the user group (“users”) if they used either the medication timeline or emotional tracking features of the app. Patients who downloaded the app but did not use either of these two key features (but may have used other features like FAQ) or declined to use the app were assigned to the non-user group (“non-users”) (see Robertson et al. 2022(8))

2. Participant demographics and treatment characteristics

The participant demographics and treatment characteristics data collected from the clinic database for use in this linkage analysis included patient age, Anti-Mullerian Hormone (AMH, pmol/L), cycle number, cycle outcome (number of live babies per cycle, and live birth [yes/no] per initiated cycle, and per complete cycle), number of eggs collected, and embryos cryopreserved and diagnosis.

3. *Clinical data*

3*a. Treatment return rates*

Treatment return rate was the proportion of patients, expressed as a percentage, of patients who returned and started another stimulated fresh cycle of treatment within 12 months of the failed index cycle of their complete cycle. A complete cycle was defined as all embryo transfers, including frozen, resulting from one episode of ovarian stimulation.

3b. Live birth rate (LBR)

'Live birth' (yes/no) was defined as a live born neonate. 'No live birth' included IVF/ICSI cycles that were cancelled mid-stimulation, those with failed fertilisation, no embryos for transfer, failed implantation after embryo transfer, or pregnancy resulting in miscarriage.

Procedure

At their pre-cycle nursing consultation, patients were informed how to download the app from the Google Play Store (Android devices) or Apple App Store (iPhone devices) to their smartphone and create a user account. Their profile was then populated with relevant medication information via the clinic portal, through which medication changes could also be made during the treatment cycle, as necessary.

Data analysis

Data from the emotional tracking and medication timeline features were extracted from the MediEmo app platform and then linked to the clinical data from the clinics electronic patient database IDEAS™ (Mellowood Medical) using the patient's hospital ID number. After linkage the resulting study database was fully anonymised and analysed using R software (13). For live birth and treatment return rates, data for the index and subsequent linked cycles (where relevant, e.g., subsequent thaw transfers) were used.

To examine the association between MediEmo usage and the clinical outcomes, the user and non-user groups were compared on clinical variables specifically (a) live birth rate per fresh index cycle, (b) live birth rate per complete cycle and (c) return rates for a stimulated cycle

within 12 months of an unsuccessful stimulated index cycle from a complete cycle of treatment. By a complete cycle, we mean all fresh and frozen embryo transfers resulting from one stimulated cycles of treatment. For the complete cycle analysis (b), cycles not yet yielding a live birth but having remaining frozen embryos in storage were excluded from analysis as the cycle was not yet complete. For the return rate analysis (c), only patients that had a failed complete cycle, i.e., had used all embryos generated from their index egg collection and for whom the initial fresh index cycle was more than 1 year ago were included as per definition of treatment discontinuation in a previous systematic review (14). Cycles with remaining frozen embryos or where the original fresh index cycle was undertaken less than one year ago were excluded from this analysis as the cycle was not complete or insufficient time elapsed to meet the Gameiro et al. (2013)(14) definition of discontinuation. Previous analysis has demonstrated this approach will capture 92% of those who return for a further fresh stimulated cycle within this centre (15). Statistical comparison between users and non-users was performed using Wilcoxon rank sum test as the data was not normally distributed or chi-square test (as appropriate). Associations between clinical variables (live birth, return rate) and MediEmo use, controlling for confounders (i.e., demographic characteristics), were further examined using logistic regression. The full interaction model (Model 1) was fit first and included age as a potential confounder, MediEmo use, and the interaction between age and MediEmo use to examine whether it moderated any significant association between MediEmo use and outcomes (live birth or return rate). Model 2 included age and MediEmo use only, without interaction. The final model, Model 3, included only the age to examine whether removing MediEmo use significantly reduced the fit of the model predicting outcome. The decrease in fit between models was examined using likelihood ratio tests with p values and the Akaike Information Criterion (AIC). The AIC is a measure of fit (penalised for the number of parameters i.e., variables in model); a lower value is better fit. Continuous confounders were centred, and effects coding was used for dichotomous predictors. Odds ratio and 95% confidence interval were reported. The criterion for statistical significance was $p<.05$.

Results

1) MediEmo app use

Of 1280 patients seen in clinic, 1081 were eligible to use MediEmo app for a fresh stimulated cycle, and of these 863 were categorised as users and 218 as non-users. All the users used the medication management component and none of the users used only the emotional tracking. The median number of days of emotional tracking during the treatment cycle was 6, with a

mean of 8.73 days (Standard deviation 8.74). Usage of the medication management component of MediEmo showed 12.7% using the medication timeline on just 1 or 2 days and 77.7% on 12 days or more (See Table 2 in Robertson et al., 2022(8)).

2) Patient demographics and treatment characteristics

Table 1 shows descriptive and inferential statistics for patient demographics (i.e., age), treatment characteristics and clinical outcomes according to user group. MediEmo users were significantly younger than non-users, and users included fewer people with social infertility than non-users. The user groups did not differ significantly on the number for whom it was a first IVF cycle at the centre, AMH, number of eggs collected, or number of embryos cryopreserved. For clinical outcomes, there was a significantly higher live birth rate (LBR) in MediEmo users compared to non-users in the stimulated index cycle, but the LBR per complete cycle was not significantly different between groups (See supplementary Table 1 for further detail on cycle outcome according to user group).

Table 1.

Descriptive and inferential statistics for patient demographics, treatment characteristics and treatment outcome data for MediEmo users and non-users

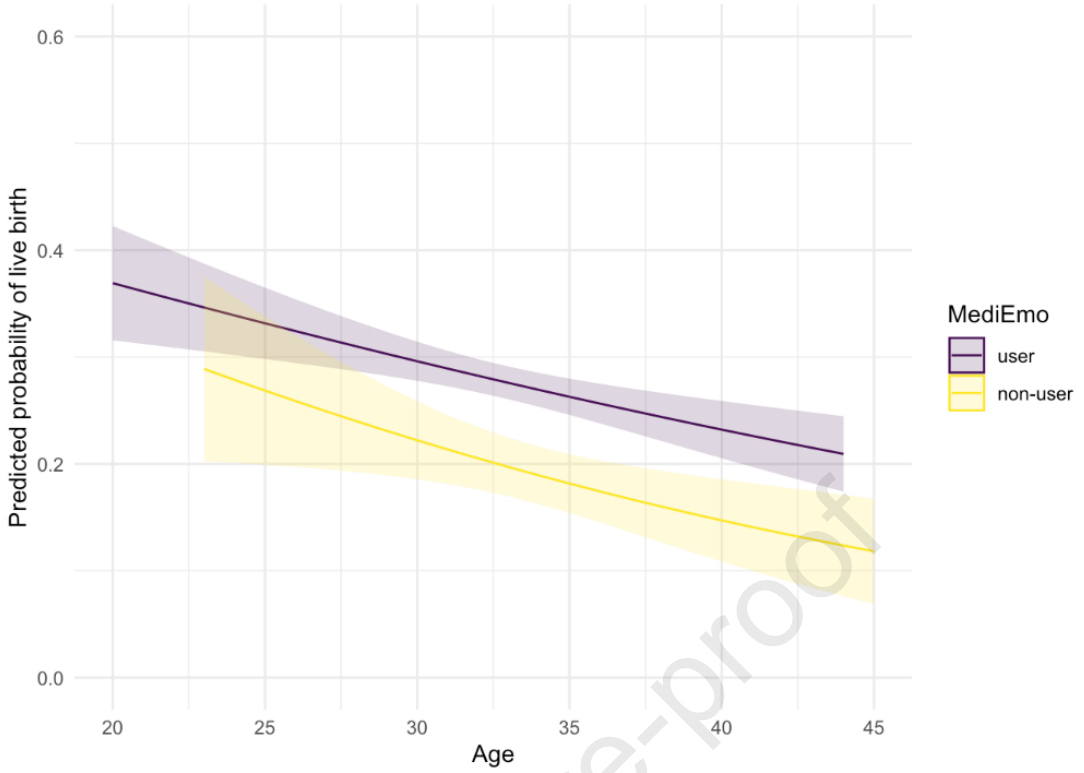
Variable	**Users** (n=863)	**Non-users** (n=218)	Wilcoxon rank sum test/ Chi^2 for binary values, p value
First IVF cycle at this centre, % yes (n)	86.91% (750/863)	87.61% (191/218)	0.869
Age in years, mean (SD)	32.80 (4.43)	33.89 (4.63)	0.001
Diagnosis % (n)			0.007
Female factor	30.36 (262)	29.36 (64)	
Diminished ovarian reserve	4.29 (37)	5.05 (11)	
Male factor	24.33 (210)	23.85 (52)	
Severe Male factor	3.01 (26)	2.29 (5)	
Unclassifiable/other	.35 (3)	.46 (1)	
Unexplained	30.48 (263)	23.39 (51)	
Social infertility	7.18 (62)	15.60 (34)	
AMH (pmol/L) mean (SD)	23.59 (22.43)	21.34 (19.48)	0.421
Number of retrieved oocytes mean (SD)	12.07 (8.30)	11.68 (8.32)	0.472
Number embryos cryopreserved mean (SD)	1.77 (2.55)	1.73 (3.02)	0.418

Live birth rate (LBR) per cycle started, % with live birth	27.81% 240/863	19.26% 42/218	0.013
LBR per complete cycle, % with live birth (n)	46.32% 359/775	38.78 76/196	0.069
Return rate for repeat fresh cycle within one year after a failed complete cycle of treatment, % yes (n)	46.56% 169/363	31.37% 32/102	0.009

Note. SD=standard deviation, AMH=Anti-Mullerian hormone. LBR=live birth rate. All values to two decimal points except p-values.

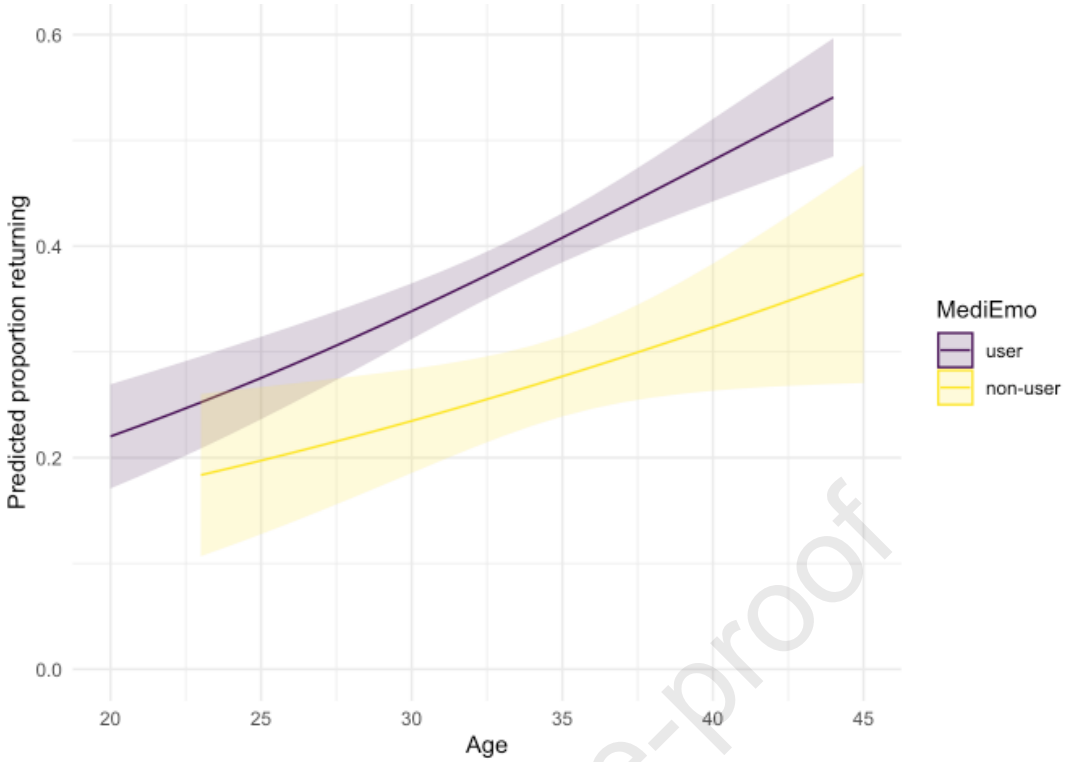
3) Use of MediEmo app is associated with live birth on the index cycle and treatment return rates after the index cycle

Supplementary Table 1 and 2 show results of model testing with logistic regression for live birth resulting from a stimulated index cycle and treatment return rates, respectively. The logistic regression for live birth rate (Supplementary Table1) controlling for age showed MediEmo use was significantly associated with live birth on the index cycle (OR=1.246 95% CI: 1.040, 1.507) when controlling for age, and the interaction between age and MediEmo use (Model 1). The interaction (age X MediEmo use) was not significant (OR=1.009 95% CI: 0.969, 1.051) in Model 1 which means there was little evidence that age of participants moderated the significant association between MediEmo use and live birth. Eliminating MediEmo use from the model (Model 3) produced a significantly worse model fit (p= 0.016) and an increased AIC (+3.807) from Model 2. The best fitting model by AIC was Model 2, with MediEmo use remaining significant after controlling for age (OR=1.2484 95% CI: 1.01, 1.509). Figure 1 shows the predicted probability of live birth for MediEmo users and non-users according to age. It was not possible to control for diagnosis using fixed effects logistic regression due to multiple diagnostic cell sizes < 5. However, controlling for diagnosis using generalized linear model showed no marked effect of diagnosis on results reported here (see Supplementary table3).



[insert Figure 1 legend about here]

Logistic regression for treatment return rate (Supplementary Table 2), showed MediEmo use was significantly associated with returning for a further stimulated cycle within one year of a failed stimulated index cycle. The best-fitting model for return rate was Model 2 which showed MediEmo use to be significantly associated with a higher return rate controlling for age (OR=1.339 95% CI: 1.092, 1.656). The interaction between age and MediEmo use was not significant (OR=1.008 95% CI: 0.964, 1.052). Removing MediEmo use from the model significantly decreased fit index (p=.005) and increased AIC (+5.96). Figure 2 shows the probability of returning for MediEmo users and non-users according to age. As with live birth rate it was not possible to control for diagnosis using fixed effects logistic regression due to multiple diagnostic cell sizes < 5. However, controlling for diagnosis using generalized linear model showed no marked effect of diagnosis on results reported for return rate (see Supplementary 4).



[insert Figure 2 legend about here]

Discussion

MediEmo use was associated with higher live birth rate (per fresh index cycle) and higher rate of return for further fresh IVF treatment after an initial failed cycle of treatment, after controlling for age, compared to non-users. This finding suggests MediEmo use could have benefits on clinical outcomes beyond simple tracking that need to be investigated with appropriate randomised designs in future research. These findings suggest that engagement with mobile applications should be supported. However, replication is needed considering factors not controlled in the present study.

The positive association between MediEmo use and clinical outcomes is in keeping with the MediEmo logic model, but the use of an observational design means other uncontrolled factors associated with app use and clinical outcomes could explain this association. Many system and individual characteristics have been associated with the uptake of digital resources (e.g., accessibility, cost, trust, digital literacy, attitude toward technology, cognitive ability) (16). Our previous reports indicates that reasons for declining to use the app (2.5% of those eligible, n=28(8)), were related to a language barrier, disability, unsuitable or old mobile phone, and preference for a telephone call, supporting these general findings. Probably the most relevant of these to the clinical outcomes are age, ethnicity, and socioeconomic status

(16) as these have been shown to be associated with the probability of pregnancy or return rates (17)). The clinic did not record ethnicity or socioeconomic level, and these would need to be investigated in future research as such differences may exist. For example, we did find more cases of social infertility in the non-user group than the user group and this may be because people using fertility treatment for social reasons (e.g., same sex couples, single people) often do not perceive themselves as infertile. As such they may not feel the same need for the MediEmo digital resource as other people with biological problems blocking their fertility. We do not think this would explain the association between MediEmo use and clinical outcomes, because the reverse would be expected; those seeking treatment for social reasons (i.e., those without biological problems) might be expected to have higher not lower fertility rates than other diagnostic groups.

In the present study, users and non-users did not differ on experience with the IVF centre, ovarian reserve marker and treatment characteristics (e.g., number of eggs collected, cryopreserved embryos). Users were younger than non-users but the association between MediEmo use and clinical outcome remained after controlling for age. It also remained significant when we controlled for age as a moderator indicating that association was not simply due to younger ages using the app more than older ages. Controlling for diagnosis also did not change results reported. While confirmatory research is needed, the results suggest that MediEmo app use could confer benefits beyond practical medication and mood tracking which need to be investigated in future research alongside a more in-depth examination of other potential confounders. A randomised controlled trial and process evaluation could examine efficacy and point to which aspect of the app (e.g., medication reminders, mood tracking, information) is most associated with benefits to elucidate fully the determinants of the association between the use of the MediEmo app in fertility care and clinical outcomes.

According to the MediEmo logic model (see Supplemental Figure 1), the positive associations between use, live birth and treatment return rates could be the result of using the different components of the MediEmo app. The link between the psychological burden of treatment and treatment discontinuation is well established (18). Therefore, use of the mood management component and its associated coping and information resources, which have been previously demonstrated to reduce the psychological burden of treatment (19), could be a main contributing factor to the positive association observed between use and clinical outcomes. A recent randomised controlled trial showed that information alone could significantly increase satisfaction and knowledge, but clinical outcomes were not investigated (20). The higher use of the medication management than emotional component also suggests that medication adherence could be an additional explanation. A systematic review noted widely varying rates of adherence in fertility care (range 28% to 81%) lending support to this

possibility, but none of the studies examined adherence in stimulated cycles (21). Whether the association is due to use overall, or use of the specific components of the app should be, as noted, an area for future explorative research but both could be contributing. The focus in this paper is MediEmo but other digital resources having similar features should also be investigated.

Despite an association with higher live birth rate on the fresh index cycle and higher return rates, descriptive statistics showed that the difference between users and non-users for the complete cycle live birth rate was not significant (41% users Vs 35% non-users) though the association was in the expected direction. An association between multiple complete cycles and higher cumulative pregnancy rate is expected and well established (22). Given the effect size we were underpowered but other factors could explain the lack of effect on the complete cycle not captured in the present study (e.g., underlying differences in embryo quality in thaw cycles). Future research should be inclusive of variables hypothesised in the path to impact on clinical outcomes to fully capture benefits of digital tools such as MediEmo, for example reduction of burden via impacts on stress hormones ((23) or via behavioural mechanisms (e.g., predictors of return rates) (24). Additionally, were the association between MediEmo use and clinical outcomes be confirmed it would be worthwhile to determine when and how such tools could be introduced to patients. Recent research suggests that IVF practice should pivot toward multicycle planning versus current norms of single cycle planning (25-27) and availability of digital apps such as MediEmo that are associated with return rates could bolster willingness to engage with this normative change.

Increasing patient and staff interest and engagement with MediEmo, particularly the emotional tracking, is key to maximising the reach and functionality of this and other digital support apps. As we discussed previously, engagement with the emotional component (>60%) was higher than typically reported for in-person support (4). Iterative improvement, with responsiveness to patient feedback and co-production of any new features is likely to increase this utility. For example, a problem identified with MediEmo in our previous work was that patients who entered emotional scores representing distress felt not enough was done with this information (‘Whilst I liked logging my mood each day there was no feedback or any further discussion over this or the results’, Robertson et al. 2022 (8), Supplementary Materials and methods, p.3). It is imperative that algorithms are optimised to ensure that when patients record struggling with the emotional impact of their IVF cycle, that this signal is acted upon by the clinic so that health care professionals can provide support in a timely manner. MediEmo app has an algorithm to trigger patient support, but future research needs to ensure thresholds set to levels at which patients feel supported. This is a challenge that concerns eliciting patient preferences, selecting the best variables for optimisation/personalisation and

dealing with implementation factors enabled with artificial intelligence and machine learning (28). Using the MediEmo to improve communication between patients and staff is one of the current developments in progress for the app.

Strengths and limitations

There are several limitations to this study. Due to its observational nature, we can only describe association between MediEmo app and recorded variables at a single institution and are unable to imply causation of the observed difference between users and non-users. Efficacy testing will be a critical next step in establishing whether the MediEmo results in causal change in behaviour and reproductive clinical outcomes. A multicentre RCT of the effect of MediEmo on treatment return and live birth rates would be beneficial, but such an RCT would need to recruit a large sample and have a prolonged period of follow up to reliably assess live birth, return rates after a failed complete cycle of treatment (i.e., minimum, 12 months per patient) and live birth rate per complete cycle. There is also a need for randomisation to control for the many potential confounders we have highlighted in the discussion (29). Although our controlled analysis suggested the confounder age was not likely to be a principal cause of associations with live birth and return rates, we acknowledge that more confounders (e.g., socioeconomic status, ethnicity, infertility duration, previous births, BMI, previous miscarriages) should be included in future research. Usage statistics reported elsewhere (4) demonstrated that non-app use was more likely due to accessibility issues as mentioned. In this study we also saw that people with social infertility were less likely to use the MediEmo application. Such results are important when considering the associations found and whether they are the result of app usage or individual characteristics. As suggested previously, the associations found may be due to sample bias. For example, patients who use mobile applications may be more motivated to engage and comply with treatment and more financially able and likely to return for treatment after experiencing an unsuccessful cycle. Similarly, patients who perceive themselves to have a better treatment prognosis may be more likely to return for treatment after an unsuccessful cycle. Future research should therefore consider the impact of patient socio-demographics and measure treatment motivation and perceptions of treatment success. Again, this highlights the importance of undertaking an RCT and not relying solely on formative studies especially that RCTs of digital health interventions have been shown to at times overturn conclusions made from observational or non-randomised studies (30). A definitive RCT trial can only be undertaken once and is best performed only when the digital tool is relatively stable, can be implemented with high fidelity and the overall benefits expected to be clinically meaningful (31). Cost-benefits of implementation could also be examined in such trials as recent evidence suggests high return rates for cognitive-type interventions like MediEmo (32). The development and early

evaluation phase of the MediEmo app has demonstrated good user experiences, relevant association with proposed outcomes, suggesting it can be moved to the next stages of evaluation.

Conclusion

Digital tools, including apps, are increasingly used alongside fertility and other medical treatments. Our study on MediEmo use demonstrates that if app development draws on existing research evidence and focuses on patient and staff needs and preferences, it is possible to develop a practical, easily scalable tool, leading to high uptake and the possibility of measurable benefit to patients.

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Figure legends

Figure 1. The probability of live birth per fresh index cycle for MediEmo users and non-users controlling for age. Colour indicates MediEmo use (purple = users, yellow = non-users), width of shading around each line indicates standard error of the estimate of the predicted probability.

Figure 2. The probability of returning rate within 12-months of a failed fresh (index) cycle for MediEmo users and non-users controlling for age. Colour indicates MediEmo use (purple = users, yellow = non-users), width of shading around each line indicates standard errors of the estimate of predicted probability.

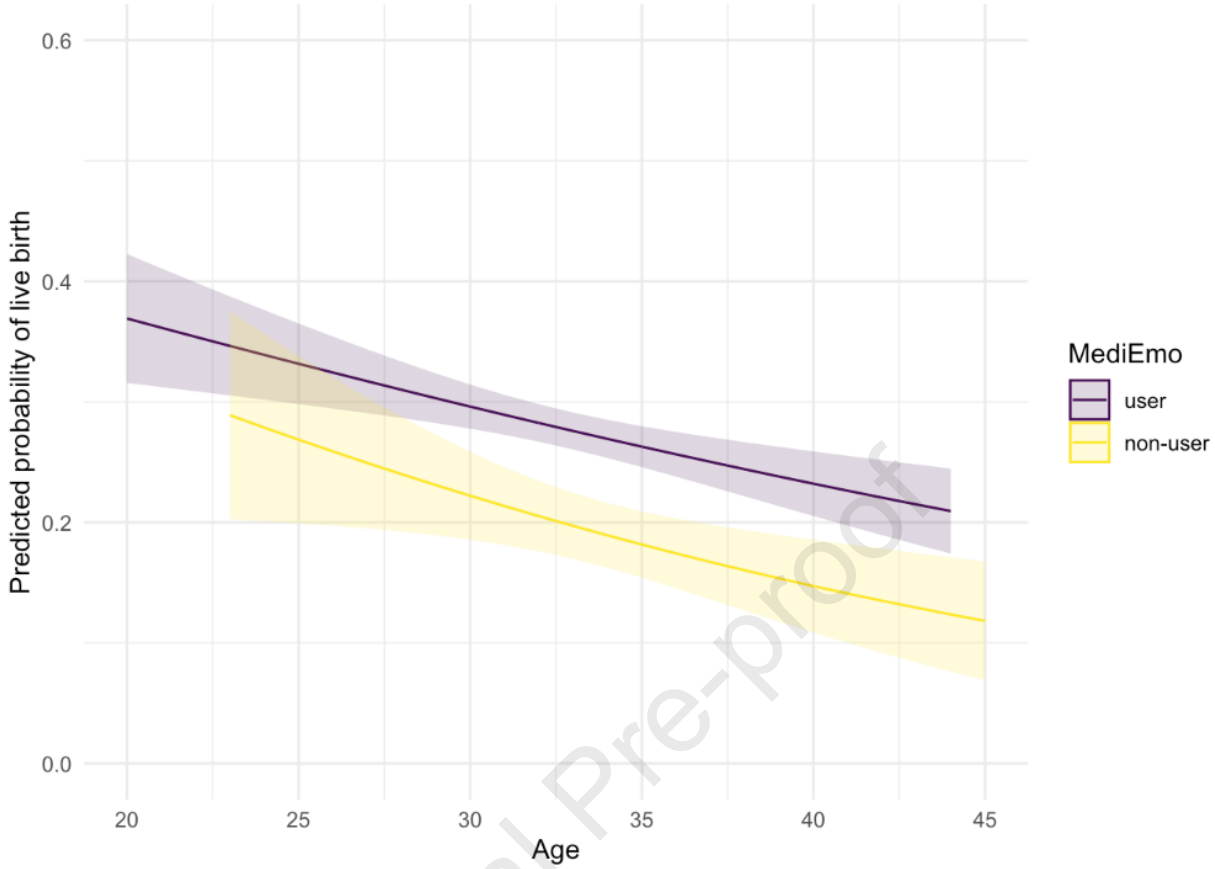
Supplementary Figure 1. The logic model for MediEmo. The model shows how the MediEmo app is intended to work. The inputs are implemented via a set of activities within MediEmo that are expected to lead to better adherence to medication, time savings for patients and staff over uncertainties, a more supportive environment with better patient trestment tolerability and resilience during treatment. These outputs are expected to lead to a better and more efficient service, and higher treatment continuation and pregnancy rates.

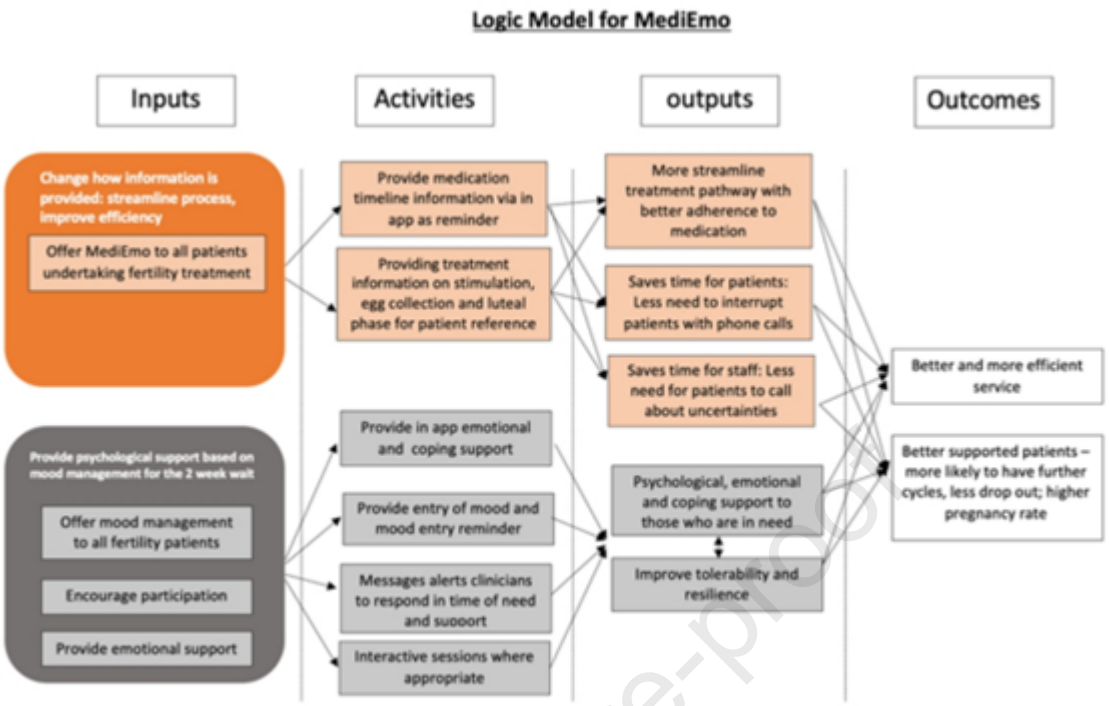
Table 1.

Descriptive and inferential statistics for patient demographics, treatment characteristics and treatment outcome data for MediEmo users and non-users

Variable	**Users** (n=863)	**Non-users** (n=218)	Wilcoxon rank sum test/ Chi^2 for binary values, p value
First IVF cycle at this centre, % yes (n)	86.91% (750/863)	87.61% (191/218)	0.869
Age in years, mean (SD)	32.80 (4.43)	33.89 (4.63)	0.001
Diagnosis % (n)			0.007
Female factor	30.36 (262)	29.36 (64)	
Diminished ovarian reserve	4.29 (37)	5.05 (11)	
Male factor	24.33 (210)	23.85 (52)	
Severe Male factor	3.01 (26)	2.29 (5)	
Unclassifiable/other	.35 (3)	.46 (1)	
Unexplained	30.48 (263)	23.39 (51)	
Social infertility	7.18 (62)	15.60 (34)	
AMH (pmol/L) mean (SD)	23.59 (22.43)	21.34 (19.48)	0.421
Number of retrieved oocytes mean (SD)	12.07 (8.30)	11.68 (8.32)	0.472
Number embryos cryopreserved mean (SD)	1.77 (2.55)	1.73 (3.02)	0.418
Live birth rate (LBR) per cycle started, % with live birth	27.81% 240/863	19.26% 42/218	0.013
LBR per complete cycle, % with live birth (n)	46.32% 359/775	38.78 76/196	0.069
Return rate for repeat fresh cycle within one year after a failed complete cycle of treatment, % yes (n)	46.56% 169/363	31.37% 32/102	0.009

Note. SD=standard deviation, AMH=Anti-Mullerian hormone. LBR=live birth rate. All values to two decimal points except p-values.





Logic Model for MediEmo