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ORIGINAL ARTICLE

Women's perspectives on ovulation induction with or without IUI as treatment for normogonadotrophic anovulation: a discrete choice experiment

N.S. Weiss[1,2], A.M.F. Schreurs[1], F. van der Veen[2], P.G.A. Hompes[1], C.B. Lambalk[1], B.W. Mol[3], and M. van Wely [2,*]

[1]Center of Reproductive Medicine, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands [2]Centre of Reproductive Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands [3]The Robinson Research Institute, School of Pediatrics and Reproductive Health, University of Adelaide, Norwich Centre, 55 King William St, North Adelaide SA 5006, Australia

*Correspondence address. Centre of Reproductive Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam-Zuidoost, The Netherlands. E-mail: m.vanwely@amc.uva.nl orcid.org/0000-0003-1682-6862

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STUDY QUESTION: What are the treatment preferences of women with normogonadotrophic anovulation treated with ovulation induction with or without intrauterine insemination (IUI)?

SUMMARY ANSWER: Women with normogonadotrophic anovulation differ in their treatment preference; half of them base their preference on the lowest burden and half of them on the highest effectiveness.

WHAT IS KNOWN ALREADY: Common treatments for anovulatory women who wish to conceive are ovulation induction using clomiphene citrate or letrozole taken in tablet form or with injections containing gonadotrophins, all optionally combined with IUI. Patient preferences for these alternatives have not yet been examined in these women.

STUDY DESIGN, SIZE, AND DURATION: Between August 2014 and February 2017 we conducted a multicentre discrete choice experiment (DCE). The target sample size was calculated by including 20 women for six attributes in the main analysis resulting in the inclusion of 120 women to be able to assess heterogeneity across choices.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We invited treatment-naive women diagnosed with normogonadotropic anovulation and visiting the outpatient clinic of five Dutch centers (three teaching hospitals and two university hospitals) to participate in the DCE by completing a printed questionnaire. We asked women to indicate their preference in hypothetical alternative treatment scenarios by offering a series of choice sets from which they were to choose their preferred alternatives. The choice sets contained several treatment characteristics of interest, i.e. attributes concerning ovulation induction with clomiphene citrate or letrozole versus gonadotrophins, as well as intercourse and IUI. We selected six attributes: number of visits to the outpatient clinic during treatment; type of medication; intercourse or IUI; risk of side effects; willingness to pay; and pregnancy chances leading to the birth of a child after six treatment cycles.

We used a multinominal logit model to determine the preferences of women and investigated heterogeneity in preferences through latent class analysis. To determine if women were willing to make a trade-off for higher pregnancy rates at the expense of a higher burden, we calculated the marginal rate of substitution.

MAIN RESULTS AND THE ROLE OF CHANCE: The questionnaire was completed by 145 women. All six attributes influenced women's treatment preferences and those valued as most important were low risk of side effects, a minimal number of hospital visits and intercourse. A total of 55% of women were driven by the wish to conceive with the least medical interference and lowest burden. The remaining women were success driven and chose mainly for the highest chances to conceive, regardless of the burden. Age and

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duration of subfertility did not significantly differ between these women. Women were willing to trade-off some burden and costs for higher pregnancy chances.

LIMITATIONS REASONS FOR CAUTION: The sample size of our study is relatively small which made it not possible to perform interaction tests and subgroup analyses.

WIDER IMPLICATIONS OF THE FINDINGS: Our results may be used during the counseling of couples about their treatment options. These findings are an argument to explore if a woman prefers potentially fast success or a medically less intense route that might take longer. The preference for the less intense route would lead to the continuation of ovulation induction with oral drugs such as clomiphene citrate or letrozole rather than treatment with injected gonadotrophins, or even IVF.

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WHAT DOES THIS MEAN FOR PATIENTS?

Women who have ovulation problems, such as polycystic ovary syndrome, may be given tablets or injections to stimulate ovulation and may also be offered intrauterine insemination (IUI). This study looked at women's preferences to see what women prefer and what may influence their preferences.

Women who had just been diagnosed with an ovulation problem were invited to take part in a survey where they were presented with a range of different treatment scenarios. The factors taken into consideration included the number of visits to the clinic during treatment, the type of medication, whether they had IUI or intercourse, the risk of side effects, the cost, and finally the chances of having a baby after six cycles of treatment.

In total, 145 women filled out the survey and 55% said they would want to get pregnant with the least medical intervention and lowest burden. The others opted for the highest chance of having a baby regardless of the burden. Most women would choose to have intercourse rather than IUI but were willing to have IUI if the chances of getting pregnant rose significantly.

The researchers suggest that the findings may reflect the fact that the women included in the survey had never had any treatment in the past, but in this group the chance of pregnancy was not the only important issue in their care. They suggest that a decision-making tool for use in clinics might help when working out the preferable treatment for an individual.

Introduction

Shared decision-making begins with an understanding of patient preferences (Towle and Godolphin, 1999). There is increasing interest in patient-centeredness within reproductive medicine since patients not only value the effectiveness of a treatment but also the burden, safety and costs. The trade-offs they make can be very different between patients (Dancet *et al.*, 2014; Duthie *et al.*, 2017). Dropout rates in couples undergoing fertility treatment are reported to be ~50% and are mainly a result of emotional distress (Brandes *et al.*, 2009). Insight into treatment preferences may help to counsel the woman for an individualized treatment strategy, thereby improving patient compliance by preventing dropout (Dancet *et al.*, 2011; Pedro *et al.*, 2013).

Approximately 20% of fertility treatment concerns ovulation induction in women with normogonadotrophic normo-estrogenic anovulation, or oligo-ovulation (Brown *et al.*, 2009).

Ovulation may be induced with oral agents such as clomiphene citrate and letrozole or parenteral drugs such as gonadotrophins (NICE Fertility Guideline, 2013; Legro, 2016; Wang *et al.*, 2017). There are several meaningful differences between these medications. Although clomiphene citrate and letrozole can be taken orally, they can cause side effects. Clomiphene citrate may induce flushes and mood swings whereas letrozole can give headache and abdominal cramps. Gonadotrophins can only be administered by subcutaneous injection, but tend to have fewer side effects than clomiphene citrate (Legro *et al.*, 2014; Legro, 2016). Since the oral agents are much cheaper than gonadotrophins and monitoring of these cycles takes fewer hospital visits than monitoring cycles stimulated with gonadotrophins, the treatment with oral agents is remarkably less costly (Homburg *et al.*, 2012; Balen, 2013). Around ovulation, conception can be realized by either intercourse or intrauterine insemination (IUI) (Hughes, 1997).

To explore whether women prefer fast success or a medically less intense road that might take longer, we evaluated the treatment preferences of women with normogonadotrophic anovulation undergoing ovulation induction with or without IUI by means of a discrete choice experiment (DCE). DCEs have become a commonly applied approach over recent years (Harrison *et al.*, 2014; Kleij *et al.*, 2017). The method involves asking individuals to indicate their preference in hypothetical alternative treatment scenarios by offering a series of choice sets from which they are to choose their preferred alternatives. The choice sets contain several treatment characteristics of interest, i.e. attributes (Ryan

et al., 2001; Reed Johnson *et al.*, 2013). The attributes are commonly defined by a literature review and by the expert opinions of focus groups of health care workers who are experienced in the subject under study.

Materials and Methods

Women diagnosed with normogonadotrophic anovulation who were visiting the outpatient clinics of five Dutch hospitals and who had never undergone fertility treatment were invited to participate in the study. Being treatment-naive prevented any bias that women might have based on their knowledge and experiences with previous treatments. Women who gave their informed consent to participate in this study received a printed questionnaire with 28 fictional scenarios, presented in 14 questions. Each question consisted of two fictional treatment options. The women were asked, for each scenario, to choose their preferred treatment (Table I). The scenarios included features concerning ovulation induction with clomiphene citrate or letrozole versus gonadotrophins as well as features about intercourse and IUI. Women had to be able to understand the questionnaire, which was written in Dutch. We asked women to complete the questionnaire before starting ovulation induction or when they had just started ovulation induction. If the questionnaire had not been returned within a few weeks, we sent out a reminder.

The DCE design of this study was based on a report of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) for good research practices for a Conjoint Analysis Task Force, which is a widely used guideline for designing a DCE study (Reed Johnson *et al.*, 2013; Hauber *et al.*, 2016).

We defined the attributes in the DCE based on the expert opinions of a focus group consisting of gynecologists working in one of the participating hospitals and specialized in treating women with anovulation. Also experts on DCE testing from one of the hospitals were consulted to create the final questionnaire. We selected six attributes that were most frequently indicated by the experts: number of visits to the outpatient clinic during treatment; type of medication; intercourse or IUI; side effects; willingness to pay; and chances of the birth of a child after six treatment cycles. These six attributes cover the areas of 'burden', 'costs' and 'effectiveness'. The levels assigned to the attributes were also based on the opinion of the experts. A summary of the attributes and their features, i.e. 'levels' is shown in Table II.

Table I Example of a discrete choice question in the DCE-questionnaire.

Scenario 1	Treatment A	Treatment B
Number of hospital visits during one treatment cycle	2	4
Ovarian stimulation	Tablets for 5 days	Tablets for 5 days
Place of fertilization	Insemination at the hospital	Insemination at the hospital
Side effects per treatment	Existing	Non existing
Financial contribution	None	None
Chance of conceiving after six treatment cycles	45 out of 100 (45%)	40 out of 100 (40%)
I choose	A	B
	☐	☐

DCE, discrete choice experiment.

The six attributes and their levels generated a total of 144 ($2^4 \times 3^2$) possible scenarios. We selected an independent sample of 13 scenarios using a design meeting the main criteria for an efficient DCE design (Huber and Zwerina, 1996; Carlsson and Martinsson, 2003). We used Ngene design software to draw a most efficient design (version 1.1.1 Choicemetrics Pty Ltd, Sydney, NSW, Australia).

Next, a check for internal consistency was included by adding a dominance test comprising a total of 14 scenarios in the questionnaire. The dominance test is a treatment scenario in which one option is set to be optimal, i.e. all levels are equal to or better than the other option (Table III). Therefore, if the woman chooses the suboptimal treatment one can conclude that she does not understand the questionnaire and the results cannot be used for analysis.

We included additional questions to collect baseline characteristics, i.e. age, educational level, duration of subfertility and possible fear of injections. There was also one open-ended question for the women to endorse their answers and add comments.

Table II Attributes and levels used in the DCE design.

Attribute	Level
Number of hospital visits during one treatment cycle	0
	2
	4
Ovarian stimulation	Tablets for 5 days
	12 injections
Place of fertilization	Intercourse at home
	IUI at the hospital
Sides effects per treatment	Non existing
	Existing
Contribution	None
	€500
Chance of conceiving after six treatment cycles	40 out of 100 (40%)
	45 out of 100 (45%)
	50 out of 100 (50%)

Table III Dominance test included in DCE design for internal validity.

Scenario 4	Treatment A	Treatment B
Number of hospital visits during one treatment cycle	2	4
Ovarian stimulation	Tablets for 5 days	12 injections
Place of fertilization	Intercourse at home	Insemination at the hospital
Side effects per treatment	Non existing	Existing
Contribution	None	€500
Chance of conceiving after six treatment cycles	50 out of 100 (50%)	40 out of 100 (40%)
I choose	A	B
	☐	☐

We introduced a pilot version of the questionnaire in one of the participating hospitals, to identify any inconsistencies in the questionnaire. After receiving 20 completed questionnaires, the pilot version was tested for internal validity. The dominance test was filled in correctly by all 20 women. Basic analysis suggested our expected direction of effect for all attributes. For the attribute 'chance of conceiving' a smaller effect was seen than we expected with much heterogeneity in response. We interpreted this as being caused by the relatively small differences in levels: a 40% versus 42% versus 44% chance of conceiving. Therefore, this attribute was adjusted by enlarging the thresholds of the levels to 40% versus 45% versus 50% chance of conceiving. The 20 women had no negative comments on the DCE therefore no other changes were made. Subsequently, the DCE was expanded to the four other hospitals.

We calculated the sample size by using a rule of thumb of 20 women per attribute. Since our DCE contained 6 attributes, a minimum of 120 women was expected to be able to assess heterogeneity across choices. This was confirmed by assessing the size effect measures of the pilot data.

Statistical analyses

We estimated the importance that women placed on each attribute level using a main-effects (no interactions) multinominal logit model, as recently described (Hazlewood *et al.*, 2016). We included the attribute 'chance of conceiving' as a continuous variable. All other attributes were included as categorical variables. A statistically significant coefficient indicated that women considered that attribute important.

We investigated preference heterogeneity through latent class analysis (LCA). With LCA one can study whether women have comparable patterns of preference in order to estimate the probability that each woman belongs to a certain class (Hazlewood *et al.*, 2016). We assigned women to the latent class for which they had the highest probability. We determined the association between selected patient characteristics and latent class membership using univariable and multivariable logistic regression models. We included women's age, parity and duration of subfertility *a priori* in view of their expected preference effect to these attributes on choice-making.

Finally, we determined the increase in the chances of conceiving required for women to accept a treatment with an undesirable attribute, called the marginal rate of substitution (MRS), i.e. the trade-off that women are willing to make for higher pregnancy rates (Hazlewood *et al.*, 2016). The median and 95% CI of the MRS were estimated through Monte Carlo sampling.

All analyses were performed using SPSS 22 (IBM: IL, USA) and R (version 3.1.2; http://www.r-project.org).

Ethical approval

The Medical Ethical Committee of the Academic Medical Centrer of Amsterdam approved the use of the DCE.

Results

The study was performed between August 2014 and February 2017 in three teaching hospitals and two university hospitals in the Netherlands. A total of 234 women met the inclusion criteria and received the questionnaires. The response rate was 62%, with 145 returned questionnaires and these questionnaires were all included for analysis. The dominance question was answered correctly by all women.

Characteristics of participating women

The baseline characteristics of the women are shown in Table IV. The mean age was 30 years (range 23–40). The majority of women was highly educated (80%) and primary subfertile (81%) with a median duration of subfertility of 12.6 months. There were 29 women (23%) who reported having moderate to extreme fear of injections.

Table IV Patient characteristics of responders at inclusion.[a]

Characteristic	
Mean age in years (range)	30 (23–40)
Median duration of subfertility in months (range)	12.6 (0.9–197.6)
Characteristic	***n* (%)**
Highest level of education	
Primary	0 (0)
Secondary	29 (20.0)
Tertiary	116 (80.0)
Income	
Below average	5 (3.4)
Average	32 (22.1)
Above average	101 (69.7)
Does not want to tell	7 (4.9)
Fear of needles/injections*	
None	49 (38.3)
Some	50 (39.1)
Moderate	20 (15.6)
Severe	6 (4.7)
Extreme	3 (2.3)
Parity	
1	27 (18.6)
0	118 (81.4)

[a]Responders, $N = 145$.
*Responders, $N = 128$ (question was added during the pilot study).

Attributes defining the choice for treatment

All attributes contributed to the choice for treatment (Table V). The most important attributes were intercourse versus IUI (coefficient 1.8 [95% CI 1.61–1.99]), no hospital visits compared to four visits (95% CI 1.68 [1.97–1.51]) and having no side effects versus having side effects (coefficient 1.68 [95% CI 1.8–1.46]). The chances to conceive showed a linear effect with women's preferences; for every 1% increase in chance, the coefficient increased by 10% (coefficient 0.10 [95% CI 0.075 to 0.125]).

Preference heterogeneity

LCA identified two subgroups of women. Over half of the women (Latent Class 1; 55%) preferred tablets over injections, having no side effects, no hospital visits and intercourse over IUI. The remaining women (Latent Class 2; 45%) chose mainly for the highest chances to conceive despite the need for injections, possible side effects and more hospital visits. Coefficients per attribute for both subgroups are shown in Table V.

We performed a univariable analysis on the characteristics 'age' and 'duration of subfertility' within the LCA. The women of Latent class 1

were on average 4 years younger and their duration of subfertility was on average 3 months shorter; these differences were not statistically different ($P = 0.24$ and 0.37 respectively, Table VI).

The MRS

The MRS analysis showed that women were willing to accept injections over tablets for an increase of 6.8% in the chances to conceive. Two hospital visits per treatment cycle versus no visits as well as personal costs of €500 were accepted if there would be an 8.9% increase in the chances to become pregnant.

For the presence of side effects, requiring four hospital visits per cycle and IUI versus intercourse the trade-offs for the chance of pregnancy were 14, 14 and 15%, respectively (Table VII).

Discussion

This preference study among 145 women with normogonadotrophic anovulation who wished to conceive showed that all six selected attributes played a significant role in their preferences for treatment. Three attributes were valued as most important: low risk of side effects, a minimal number of hospital visits and intercourse. A small majority of women was driven by the wish to conceive with least medical interference and lowest burden, while the other women were primarily success driven and chose mainly for the highest chances to conceive. Age and duration of subfertility did not significantly differ between these women. Women were willing to trade-off some burden and costs for higher pregnancy chances.

A strength of our study is that it was designed following the checklist of the report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force (Reed Johnson *et al.*, 2013). In addition, we performed a pilot study after which we made appropriate adjustments to the DCE. All women answered the dominance test correctly, which is why we assume that the questionnaire was easy to understand for the women, most of whom were highly educated. Another strength is that we solely included treatment-naive women; our rationale was that women who had previously undergone one of the treatments either successfully or unsuccessfully, may answer the questionnaire with a strong preference or dislike for one or the other treatment without actually considering the different features.

The main limitation of the present DCE is its relatively small sample size. For a full DCE, including interaction tests and subgroup analyses, a sample size of at least 500 women would be required. Another limitation is that the response rate was only moderate, possibly leading to

Table V Multinominal regression analysis and two latent class analyses.

Attributes	Multinominal regression		Latent class 1 55%		Latent class 2 45%	
	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Intercept	−7.65		−7.67		−7.64	
Chance of conceiving per 1% (40–50%)	0.12	0.095 to 0.15	0.075	0.039 to 1.11	0.16	0.11 to 0.21
Side effects (yes versus no)	−1.68	−1.80 to −1.46	−1.89	−2.17 to −1.61	−1.37	−1.62 to −1.12
Stimulation (injections versus tablets)	−0.83	−0.99 to −0.66	−1.41	−1.78 to −1.04	−0.35	−0.02 to −0.68
Number of hospital visits						
0	Ref.	−1.33 to −0.81	Ref.	−1.97 to −1.03	Ref.	Ref.
2	−1.07	−1.97 to −1.51	−1.50		−0.87	−1.05 to −0.59
4	−1.68		−2.35	−2.86 to −1.85	−1.20	−1.53 to −0.87
Intercourse versus IUI	1.80	1.61 to 1.99	2.71	2.26 to 2.09	1.13	0.66 to 1.60
Costs versus no costs	−1.08	−1.26 to −0.88	−1.13	−0.83 to −1.43	−0.84	−1.14 to −0.54
2 log likelihood	−611			−582		
Pseudo R^2	0.322			0.328		
cAIC*	1185			1102		

*cAIC, consistent Akaike Info Criterion.

Table VI Two latent class analyses: patient characteristics.

Patient characteristics	Latent class I	Latent class II	Univariable analysis
	55% of women Mean (95% CI)	45% of women Mean (95% CI)	*P*
Age (years)	28.2 (25.0–31.5)	32.1 (29.0–35.2)	0.24
Duration of subfertility (months)	8.2 (6.0–10.4)	11.3 (8.9–13.7)	0.37

Table VII Marginal rate of substitution.

		% Increase in chance of conceiving to accept the undesirable attribute
		Overall (95% CI*)
Attribute	**Level**	
Side effects	Yes versus no	14 (9.7–18)
Injections	Yes versus no	6.8 (1.9–12)
Number of visits	2 versus 0	8.9 (3.4–14)
	4 versus 0	14 (7.2–21)
Place of fertilization	IUI versus intercourse	15 (8.3–22)
Costs	€500 versus no costs	8.9 (3.2–15)

*CI interval was based on the Krinsky Robb method adjusted for class probabilities.

selection bias. On the other hand, our sample size, composition of the population and response rate is comparable with other recently published DCEs, which is why we assume that our data are more widely applicable (van den Wijngaard *et al.*, 2015; Hentzen *et al.*, 2017).

Finally, our cohort is quite homogeneous including mainly highly educated women earning an above average income. Since women with a high educational level and income are less likely to have a positive perspective on care, whereas women with a lower occupational status experience more anxiety, our results may not necessarily extrapolate to all women (Dancet *et al.*, 2010; Gameiro *et al.*, 2015). Also, the facts that our population had easy access to fertility care (as most fertility clinics offer ovulation induction) and that IUI is reimbursed in the Netherlands have to be taken into account when generalizing the data.

There are no previous studies on women's preferences in the treatment of anovulation comparing oral agents with gonadotrophins, both with or without IUI. There is one preference study using interviews with women with clomiphene citrate-resistant polycystic ovary syndrome comparing gonadotrophins with laparoscopic electrocautery of the ovaries (Bayram *et al.*, 2005). There are two studies on subfertile women with various underlying causes, one of which used DCE-techniques and the other examined willingness to pay and conjoint analysis. All three preference studies show that pregnancy rates are the leading factor for women when deciding on a specific treatment (van Empel *et al.*, 2011a, 2011b; Palumbo *et al.*, 2011). In contrast, in our study the majority of women chose mainly an approach with the lowest treatment burden. This discrepancy with the previous studies is probably caused by the fact that we, unlike the other studies, examined treatment-naive women. It seems likely that women who have experienced numerous failed treatment cycles, as was the case in the other studies, prefer a treatment with a high success rate and would therefore accept a fair amount of burden. This concept is supported by the comments found in the open-ended question of our DCE (data not shown).

Our results emphasize that effectiveness, i.e. pregnancy chances, are not the sole important issue in fertility care. This supports the outcomes of a focus group study, a survey study and a systematic review that found that aspects such as having a lead physician, seeing trained fertility nurses, physical comfort, accessibility and information provision can help to improve women's satisfaction with fertility treatment and care (Dancet *et al.*, 2010, 2012; van Empel *et al.*, 2011a, 2011b). This, in turn, may prevent women dropping out of treatment (Pedro *et al.*, 2013).

In our study, most women preferred having intercourse over IUI but were willing to accept IUI when pregnancy chances rise significantly. This trade-off is comparable with the results of a preference study that examined subfertile couples and their preferences on insemination (Steures *et al.*, 2005). On the subject of IUI, we must take into account the present discussion on the effectiveness of this treatment (Nahuis *et al.*, 2013; Tjon-Kon-Fat *et al.*, 2016).

Implications for practice and future research

The results of our study can be used during the counseling of couples about their treatment options. We suggest the development of a simple, practical decision tool that can help to distinguish the personal preference of an anovulatory woman consulting a fertility clinic before she starts treatment. These findings are an argument to explore whether a woman prefers possible fast success (i.e. time to pregnancy) or a medically less intense route that might take longer. The preference for a less intense route would lead to the continuation of ovulation induction with oral drugs, such as clomiphene citrate or letrozole, rather than treatment with gonadotrophins or even IVF.

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Authors' roles

N.S.W. and M.v.W. designed the DCE, N.S.W. was in charge of collecting data, M.v.W. performed the analyses. N.S.W. and A.M.F.S. took the lead in writing the manuscript, F.v.d.V., P.G.A.H., C.B.L., B. W.M. and M.v.W. helped with interpreting the outcomes of the data and reviewed the manuscript. All authors read, edited and approved the final manuscript.

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Conflict of interest

C.B.L. reports grants from Merck and Ferring. B.W.M. reports consultancy for Merck, ObsEva and Guerbet.

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