Perspectives of mild cycle IVF: a qualitative study

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INTRODUCTION

Developments in the field of IVF in the past decade or so have heralded the introduction of new forms of mild ovarian stimulation protocols. Clinical debate has centred around such issues as whether the milder protocols (or as it is referred to in New Zealand, ‘short cycle IVF’) meet traditional parameters of success (when compared with conventional stimulation protocols), and whether mild IVF contributes to a more ‘patient-friendly’ treatment regime, one that is physically and emotionally less stressful and harmful than conventional IVF (Heijnen et al., 2004). At present, conventional IVF continues to dominate clinical practice worldwide (Verberg et al., 2009) and clinical uptake of mild protocols has been gradual (Fauser et al., 2010). This qualitative thematic analysis study examined women’s attitudes and beliefs regarding mild cycle IVF with the aim of providing insight for practitioners and fertility consumer groups.

BACKGROUND

Conventional IVF protocols involve the use of co-treatment with gonadotrophin-releasing hormone (GnRH) agonist medications which ‘down-regulate’ the pituitary gland, before stimulating it again in order to maximize the number of oocytes retrieved (Heijnen et al., 2007; Fauser et al., 2010). Maximizing oocyte retrieval has previously been considered necessary to create the best possible chances of conception (Fauser et al., 2010), thus creating the premise that the greater the number of oocytes retrieved, the greater the chances of a successful outcome (Verberg et al., 2009). This treatment generally involves 3 weeks of GnRH agonist treatment along with up to 2 weeks of daily FSH injections, combined with several clinic visits and ultrasounds (Collins, 2009).

Yet, conventional IVF regimes are not without side effects and risks. One of the risks associated with a conventional IVF protocol is ovarian hyperstimulation syndrome (OHSS), which although rare, is potentially life threatening (approximately one death in 400–500 000 cycles) (de Klerk et al., 2006; Heijnen et al., 2007; Devroey et al., 2009). Further side effects which can occur alongside the down-regulation necessary for conventional treatment protocols include abdominal discomfort, depressed mood, headaches, and lower back pain and muscular pain (de Klerk et al., 2006; Pennings and Ombelet, 2007). There is also some evidence that agonist treatment contributes to anxiety and mental distress (Pennings and Ombelet, 2007; Devroey et al., 2009; Barri et al., 2010). Medical literature has also linked GnRH agonist use with depression, with studies indicating that

METHODS: In this qualitative thematic analysis study, 17 women, and 2 partners were interviewed regarding their perceptions of ‘mild’ cycle IVF. Data were thematically analysed to identify the key aspects of participants’ perceptions.

RESULTS: Participants reported that ‘mild’ cycle IVF offered a number of positive aspects, including the reduction in the intrusion of IVF procedures in women’s lives, the short timeframe spent in awaiting the results and the way mild cycle worked with women’s natural hormonal cycles.

CONCLUSIONS: ‘Mild’ cycle IVF was perceived positively by the participants particularly in terms of timeframes and the impact on their physical and emotional wellbeing.

Key words: mild cycle IVF / conventional IVF / qualitative research
between 75 and 80% of patients on this type of medication exhibited depressive symptoms (Wilkins et al., 2010). Mental distress may be related to unsuccessful IVF cycles, the side effects associated with down-regulation and/or the impact of hormone injections (Devroey et al., 2009). However, it is also difficult to differentiate from the mental distress experienced by living with infertility (Greil et al., 2010). Long-term anxiety about the possible health effects of repeated IVF medication may also represent a concern for some patients (Pennings and Ombelet, 2007; Verberg et al., 2009).

Conventional protocols require intensive monitoring. In addition, injections extend for a greater number of weeks than in mild protocols (Verberg et al., 2009). Critics of the conventional approach have noted that the costs involved in this type of protocol, both in practical terms and to the overall health system through complications, may be considerable (Heijnen et al., 2004; Fauser et al., 2010). The length of treatment may also compound the psychological burden associated with IVF treatment, which has been cited as one of the main reasons why couples discontinue treatment, even when such treatment is fully government funded (Olivius et al., 2004; Rajkhowa et al., 2006; Van den Broeck et al., 2009). Participants in Olivius et al.’s study often ceased treatment prior to completing two or three funded cycles, citing psychological burden as the primary reason for discontinuation. Given the cumulative nature of IVF treatment success rates, ways to keep couples in treatment can be considered opportunities for creating successful outcomes (Heijnen et al., 2007). However, regardless of the number of cycles undertaken, it is relevant to bear in mind that IVF treatment will still remain unsuccessful for ~50% of all couples (Heijnen et al., 2004).

In contrast to conventional protocols, mild IVF protocols utilize a GnRH antagonist during the mid to late stage of a woman’s natural cycle, thus making use of the body’s natural rise in FSH, rather than suppressing it through down-regulation (Eijkemanns et al., 2006; Verberg et al., 2009). Oocyte retrieval is generally limited to fewer than eight. Thus, mild protocols involve less complex procedures and a shorter time period for treatment (Fauser et al., 2010). A recent Cochrane Review of 45 randomized controlled studies has found that GnRH antagonist IVF cycles had a significantly lower occurrence of severe OHSS and a similar live birth rate to conventional cycles (Al-Intany et al., 2011).

Accordingly, the potential advantages of a mild stimulation protocol are thought to include lower discontinuation rates due to the fact that the mild treatment is considered more tolerable for patients. This increased tolerability is thought to be in terms of reduced monitoring and avoiding the need for down-regulation, often associated with undesirable side effects (Heijnen et al., 2007). In a randomized controlled trial comparing a mild treatment with a conventional treatment, the mild group demonstrated lower rates of depression following treatment failure, and lower dropout rates (de Klerk et al., 2006; Heijnen et al., 2007). In terms of overall discomfort, the mild and conventional groups exhibited similar levels on this measure, despite the mild cycle group having undergone more treatment cycles within the year (Heijnen et al., 2007). Similarly, an earlier study found that women in the conventional group experienced higher levels of depressive symptoms and physical discomfort during the final week of down-regulation than those participants undergoing the mild cycle treatment (for whom down-regulation was not necessary) (de Klerk et al., 2006). The study also found that women in the conventional group expressed more negative affect regarding cycle cancellation than those in the mild cycle group. This was possibly due to the amount of time these women had already invested in their treatment by undergoing down-regulation, as opposed to the mild cycle group who had only experienced several days of ovarian stimulation prior to this point.

Critiques of mild cycle IVF treatment have noted its lowered success rates in terms of pregnancy outcomes (Flisser et al., 2007). However, more recent studies which take into account term live birth rates, not by comparing treatment cycle-to-cycle, but over a set period of time, have resulted in very similar outcomes (Heijnen et al., 2007). About 444 mild IVF cycles and 325 conventional IVF cycles were completed over a 1-year period with the resulting birth rates at 44.7 and 43.4%, respectively. Thus, in women aged <38 years, the outcomes were comparable. A meta-analysis of 22 randomized controlled trials, which compared the use of GnRH agonist treatment and antagonist treatment found that there was no statistically significant difference in the probability of a term live birth between the two treatments (Kolibianakis et al., 2006). Proponents of a mild cycle IVF approach note that the nature of international parameters of IVF success centre around pregnancy rates achieved per cycle, meaning that mild cycle protocols inevitably appear less successful when reported in this way (Fauser et al., 2010). Consequently, there have been calls for success to be considered in terms of live birth per treatment started, rather than per cycle (Eijkemanns et al., 2006).

New Zealand context

In New Zealand, access to publicly funded IVF cycles rests on criteria relating to a woman’s previous history of infertility, in addition to factors such as her age, smoking status and BMI. A clinical priority access criteria assessment also allocates various points for certain criteria which patients must meet (Farquhar et al., 2010). For couples meeting these criteria, public funding is available for up to two cycles of IVF. In New Zealand, IVF treatment is offered through selected private and public providers. The proportion of publicly funded versus privately funded cycles is approximately 50:50 (Farquhar et al., 2010). Currently, several New Zealand clinics purport to offer mild cycle IVF protocols as a first option for their patients, citing fewer side effects and a quicker timeframe as among the advantages of this type of approach.

Qualitative research provides rich insights into people’s experiences, and the descriptions and meanings they place on them (Pope et al., 2006). Qualitative studies have explored women’s experiences of conventional IVF (e.g. Baker, 2004; Redshaw et al., 2007). However, only one other study has explored patients’ perceptions of mild cycle IVF protocols from a qualitative perspective. Garel et al. (2009) explored the experiences of two groups of women, one undergoing conventional IVF, the other minimal stimulation IVF. The latter group perceived the mild stimulation as a ‘lighter and more natural’ treatment which involved less hormone intervention.

This study aimed to investigate couples’ attitudes and beliefs concerning mild cycle IVF, to provide useful information for practitioners involved in caring for such women and their partners, particularly in a New Zealand setting, where the popularity of mild cycle IVF protocols appears to be growing.
Materials and Methods

Ethical approval for the study was granted through the New Zealand Northern Regional Ethics Committee. Initial recruitment for the study took place through invitations sent out by clinic staff to patients who had completed a mild cycle IVF protocol. This information was obtained through identification of patient records by the staff from a local IVF clinic. Due to only six women being recruited through the clinic, a second stage of recruitment was made through a notice on two national consumer health forum websites. The web notices invited couples who had been through a mild cycle IVF treatment to take part in the study. A further 11 women were recruited by this means. In two of these interviews, the women’s partner also participated.

Depending on their geographical location, participants were either interviewed by telephone (n = 6), or if they resided locally, face-to-face (n = 11). A semi-structured interview approach was utilized. Using an interview topic guide, all participants were asked to provide an overview of their previous history of infertility and treatment. Then they were asked to describe how the mild cycle IVF protocol had affected them: socially (e.g. family, friends and work); psychologically (e.g. emotions); physically (e.g. body changes or discomforts associated with the treatment) and economically (e.g. cost of treatments). Those who had undergone both conventional and mild cycle protocols were asked to compare experiences of the two protocols. Within this semi-structured interview frame, space was given for participants to bring up topics and issues which they saw as particularly relevant to the theme of mild cycle IVF.

Interviews were conducted by the principal researcher and the research assistant. All interviews were recorded and transcribed verbatim and any identifying information was removed at this stage of the process. Participants either elected to choose a pseudonym, or were assigned one, in order to protect their privacy.

The analytic process was guided by an inductive thematic analysis approach (Pope et al., 2006). Transcripts were read and re-read to ensure familiarity with the data, and initial codes were created for every theme which appeared in the transcripts. From this detailed organization, broader codes were identified and themes grouped together. Throughout this process, the researchers met regularly to discuss the analytic process and compare identified themes. Following this, a spreadsheet of themes was created which indicated the prevalence or frequency of each theme and the relevance of it to the overall research topic.

Results

In total, 17 women and 2 partners were recruited into the study. Participants were aged between 31 and 42 years of age and had all pursued IVF treatment within the last 5 years. Of these participants, 13 had completed at least one conventional IVF treatment and one mild cycle IVF treatment. A further four participants had completed a mild cycle IVF treatment cycle only. Eight of the women had had their last cycle publicly funded and the remainder had paid privately. Eight participants were either pregnant at the time of interview, or had had a baby; nine participants had not.

Time, working with nature, accessing mild cycle IVF and financial costs, were identified as the dominant issues by the participants in relation to mild cycle IVF.

Time

For the majority of participants several aspects related to the concept of time were articulated. The first was that the shorter timeframe involved in mild IVF cycles overall, from beginning to end of the cycle, made the rigorous injection schedule more bearable.

Natalie: Because you always knew that there was an end in sight. It was only ever the twelve days or fourteen days-ish of double injections, so it didn’t seem so bad.

The phases of down-regulation, particularly ovarian stimulation, require women to have timed daily injections for several weeks. Sometimes the duration of these phases cannot be predetermined as they are dependent on the woman’s response to the drug regime. In contrast, the timeframe for mild cycle IVF is considerably shorter and known at the outset. Such knowledge makes the discomfort of daily injections more tolerable.

Another aspect was that less time was spent on a day-to-day basis engaging with the procedures involved in the mild cycle IVF treatment regime.

Lily: With the long cycle you have so many blood tests whereas with short cycle you only have maybe two at max. And that’s significant.

For the participants mild cycle IVF protocol occupied less of their time. It was less intrusive on their day-to-day lives, allowing more time to get on with their everyday commitments. This was considered particularly advantageous when considering the reduced impact of the treatment protocol on their professional and work commitments.

The reduction in overall time required for the treatment protocol also implied less time spent waiting for results. For some participants, this translated into less time spent in an emotionally distressing or anxiety provoking state.

Amelia: The worst part about IVF is that two week waiting period between putting the embryo back in and waiting for the pregnancy test . . . it’s just, that waiting and that kind of hope . . . it’s great if it works out well but if it doesn’t it’s just, that’s all you remember. But the convenience of having it shorter is, that it makes it that much easier because you don’t feel like you’ve spent two months of your life going through something, versus one month.

IVF involved considerable physical and emotional investment for the women. The shorter timeframe of the mild cycles IVF treatment was subsequently perceived as less emotionally burdensome, even mitigating some of the most difficult aspects of going through IVF treatment.

A protocol which reduced the amount of waiting to find out if they were pregnant or not was thought to be considerably less distressing by the women.

Finally, time was considered highly relevant in a wider developmental context of a woman’s reproductive ability and perceived timeframe to conceive. Being shorter in duration, women regarded mild cycle IVF treatments as having an advantage over conventional treatment, as more cycles could be undertaken in within a timeframe, should this be necessary or appropriate.

Lily: If you had more money you could do more cycles in a year . . . It’s so much quicker, maybe it’s that year. Done. That’s it.

The implication for this participant is that the emotional investment of condensed short cycles in a shorter timeframe is preferable to several conventional cycles over a longer time period. The option of being able to engage with IVF treatment over a shorter time period is
relevant in terms of the likelihood of success decreasing with a patient’s age. Therefore, being able to undergo more cycles within a shorter timeframe may have valid implications for success.

The ‘working with nature’ perception of mild cycle IVF

Some participants talked of mild cycle IVF as working alongside a woman’s natural menstrual cycle.

Belinda: So anything you can do to try and bring this treatment as close to ‘mother nature’ as possible, because that’s obviously the best science of all, or the most effective.

Here, natural reproduction was seen as the more proven method. Hence, building on the women’s natural cycle was seen to be a more beneficial and intuitively optimal means of achieving pregnancy.

For others, weighing up the advantages and disadvantages of both protocols, and the medical intervention required, made it clear that short cycle was a more favourable choice.

Millie: Why would you take drugs to put yourself into menopause and then have to have some more to stimulate yourself, if they can just do it straight with a short cycle and work with your own, beginning of your own cycle, and have, a much shorter treatment with the same potential success rate?

For these women, in weighing up the advantages and disadvantages of each type of cycle, conventional cycle seemed counterintuitive to work against the body’s natural cycle. The suppression and replication of the body’s process seemed overly chemical and complicated, particularly if the outcomes had the potential to be the same as mild cycle.

For some participants the ‘working with nature’ perception of mild cycle IVF resulted in better quality embryos. While producing fewer embryos than conventional cycle IVF, the improved embryo quality had the potential to increase their likelihood of becoming pregnant.

Amelia: It’s about the quality game. It’s not a quantity game. There only needs to be one good one. You don’t need 10 good ones.

Mild cycle IVF was perceived as being less detrimental to the overall process of becoming pregnant. While fewer eggs were produced in the cycle, their potential to create a viable embryo was greater: a significant outcome factor for the women.

Accessing mild cycle IVF

Most participants expressed a belief that in terms of outcomes, there was very little difference between a mild cycle IVF and conventional IVF protocol. This played a key part in shaping their decision to opt for a mild cycle IVF protocol.

Natalie: Both my husband and I felt that we couldn’t see the point in doing the long cycle. The stats were the same. The outcomes were the same.

When asked about their decision regarding what type of IVF cycle to have, particularly for their first round, most participants believed that they were not provided with a range of options. Rather, they followed the recommendation given to them by their specialist.

Alice: That standard long course was what we were offered to start with. They explained it as being that’s how everyone starts and then they work from there depending on how you respond and things like that. And you’d really have to push, or really have to know your stuff, do a lot of research and things to argue.

Alice highlights two points. One is the protocol of conventional IVF as the first form of IVF treatment that women undergo. The second is that she shows how dependent some women and their partners perceive themselves to be on their specialist’s recommendations. As ingenues to the IVF process, they lack the knowledge of what options exist and the confidence to make suggestions regarding their treatment options. However, participants who had undergone more than two cycles of IVF spoke of becoming more informed by their experiences and consequently felt more in a position to exercise and express their choices.

Theresa: I didn’t want to just keep on doing the same thing and get the same results. So he [the specialist] eventually agreed to go away and have a chat with some of his colleagues. The mild cycle protocol was what they came back with.

For these women, undertaking mild IVF cycle brought different critical elements into play in the IVF reproductive process which might increase their likelihood of having a baby. For them short cycle IVF was a calculated tactic to maximize their chances of becoming pregnant.

Financial costs

Authors have suggested that mild cycle IVF is less costly than conventional IVF (Heijnen et al., 2007; Collins, 2009). In terms of direct costs to patients, this was not reflected in our study. As Amelia said, ‘The cost is no different . . . the drugs they put you on to down-regulate you are the ones that only cost $200 (NZ)’. For the nine participants who had paid privately for both types of IVF protocol, they found that the cost of mild cycle IVF was only minimally cheaper. For most of these participants, financial cost did not seem to have a significant bearing on which protocol they opted for. What was more important was which protocol would be more likely to give them a successful outcome.

Discussion

Regardless of whether or not they had become pregnant through a mild cycle IVF protocol, participants in this qualitative study viewed this form of protocol in a positive light in terms it being less time-consuming and onerous.

Our study shows that women’s access to mild cycle IVF may be determined by their medical specialists, particularly for those embarking on fertility treatment. What also is of interest is that for some women who went on to have more IVF treatments, they wanted to try something different which would increase the likelihood of becoming pregnant. This often prompted them to conduct their own research and this, combined with their own knowledge and experience, provided them with more self-identified options concerning future cycles of IVF. Thus for some participants mild cycle IVF was a reasoned and strategic choice based more on the outcome rather than the experience of IVF.

Similar to the Garel et al. (2009) study, this study found that the mild cycle treatment was perceived as a lighter, more natural treatment which required less hormone intervention. Participants in
Garel et al’s study identified the use of natural processes alongside the technical process of IVF as a positive factor, a theme that was also significant in the current study. A possible implication is that mild cycle IVF may appeal to couples who want a fertility treatment that does not completely suppress and overtake the body’s own cycle. For them conventional IVF may be perceived as a highly medicalized and interventionist treatment. Understanding mild cycle IVF as working with their hormonal cycle may also facilitate women’s understanding of their own bodies from less of a deficit position, a position which can often be adopted in the experience of fertility and can be difficult for women to deal with (Throsby, 2002).

Participants also expressed a belief that mild cycle IVF protocols might be beneficial for embryo quality. Since mild cycle IVF works with a woman’s natural cycle, the ovarian physiology differs from conventional protocols and there is some evidence to suggest that mild IVF may indeed produce a more viable embryo (Nargund, 2008; Fauser et al., 2010). It is important that patients understand this issue, as it may facilitate a better understanding of the mild cycle IVF process. Such knowledge will also assist in managing patient expectations more effectively in relation to their possible disappointment at a lower number of oocytes, particularly if they have previously undergone a conventional IVF treatment.

Time spent waiting for the results of pregnancy tests following IVF treatment has been shown to impact on tension, anxiety and worry in the days leading up to the test (Boivin and Lancastle, 2010). This was echoed in the themes identified in our study, where participants emphasized that time spent waiting was an emotionally distressing aspect of treatment which was lessened by a mild cycle IVF protocol partly due to its shorter timeframe. The shorter timeframe also meant a shorter injection schedule, and fewer diagnostic tests. In this way, the invasive nature of IVF treatment protocols on one’s time and body, such as blood tests, were perceived as more tolerable and less demanding for women when undergoing mild cycle IVF. Therefore mild cycle IVF may place less psychological burden on women in comparison to conventional IVF (de Klerk et al., 2006). As suggested by Hoigard et al. (2001) such features may make repeated IVF cycles more acceptable to women.

Finally, IVF treatment is costly. (Redshaw et al., 2007), which can be a barrier to those who cannot afford it (Collins, 2009). The cost of mild cycle IVF is seen as having the potential to be (directly and indirectly) a cheaper option for clients, health care providers and society (Olivennes, 2003; Fauser et al., 2010). It must be noted that the majority of couples in this study may have come from higher socio-economic groups and for them, the difference may not have been an issue. It is possible though that couples from lower socio-economic groups, who may not be able to afford to pay privately, may view the slightly lower cost of mild cycle IVF more positively. But although it is slightly less expensive, mild IVF may still remain beyond the reach of many couples who have to pay for their fertility treatment.

Counselling has been identified as an important component of fertility treatments in providing support, education and assessment (Wischmann, 2008). Mild cycle IVF extends the repertoire of treatments for couples experiencing infertility. Counselling can add to the process of informed choice ensuring that women and their partners understand the differences between conventional and mild cycle IVF; what is entailed; the risks, benefits and outcomes of each procedure. Given the brevity of mild cycle IVF access to counselling must not be overlooked.

One of the limitations of this study included the relatively small, mixed sample of participants, some of whom had undergone both conventional and mild cycle IVF, and others who had only undergone mild cycle IVF procedures. As such they may have had a different frame of reference for comparison. Furthermore, the participants consisted of a small convenience sample recruited through one fertility clinic and two fertility websites. Initially, there may also have been a perception that the study was in some way aligned to a particular fertility clinic. There is also the probability that perceptions of treatment could have been affected by a successful or unsuccessful treatment outcome. Indeed, several participants mentioned this as a possibility. The strengths associated with this study include its qualitative research design, which allowed for the in-depth expression and capturing of themes and perceptions, thus contributing to a seemingly sparse area of qualitative research in the field of mild cycle IVF. Future research could aim to investigate specialists’ perceptions of mild cycle IVF, in particular given its slow clinical uptake (Fauser et al., 2010). It may also be useful to compare outcomes of conventional IVF and mild cycle IVF in a local setting, using a set timeframe notion of success rather than a cycle-to-cycle approach.

**Conclusion**

Mild cycle IVF protocols seem to be gaining in popularity in New Zealand, with several clinics now offering this as a first option for IVF treatment. For most participants in our study, mild cycle IVF offered a number of positive aspects related to time factors, both in terms of a reduction in the intrusion of IVF procedures in their lives, but also in the sense of containing the emotional anxiety of waiting for results to a reduced period of time. Time was understood as a precious resource in the context of women’s fertility, with the option of mild cycle affording the possibility of more cycles being undertaken within a shorter timeframe. Results also suggested that participants perceived mild cycle IVF to be more natural, and similar in cost to conventional IVF. Finally, decision-making processes to elect either conventional or mild cycle IVF were more often than not initially guided by practitioner advice, followed by an experiential expertise built up by participants over time.

**Authors’ roles**

D.P. and S.G. designed and sought funding for the study. As first investigator, D.P. was responsible for gaining ethical approval, data collection, data analysis, preparation and editing of the manuscript drafts. S.B. assisted in interviews, analysis and writing of manuscript drafts. S.G. assisted in the data analysis and the writing of manuscript drafts. G.G. assisted in recruiting and reviewed final drafts of the manuscript.

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Conflict of interest
G.G. is the medical director of Auckland Repromed.

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