Ultrasound monitoring during first-cycle treatment with clomifene citrate: a national survey of compliance with NICE

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ABSTRACT

The National Institute for Health and Care Excellence Clinical Guideline 156 advises that transvaginal ultrasonography (TVUS) should be used in the first cycle of treatment with clomifene citrate, to assess for multifollicular development and hence the risk of multiple pregnancy. This guidance is based on expert opinion rather than research evidence. We conducted a cross-sectional online and postal survey among UK-based consultant gynaecologists and fertility specialists, to explore compliance with this guideline. A total of 110 responses met the inclusion criteria. During first-cycle treatment with clomifene, 50.9% of respondents were not always using TVUS, and 21.8% never were. Clinicians who did not have immediate access to TVUS were significantly less likely to scan ($p < 0.01$). Other key factors influencing practice were, personal experience of the clinician, lack of an evidence base to support the guideline and a willingness to accept the risk of multiple pregnancy. Several respondents questioned the value of scanning the first cycle only and highlighted that over-response may be seen in subsequent cycles. This study confirms that there is variation in adherence to the guideline and uncertainty about the clinical need for scan monitoring. Further evidence to support or refute the guideline is required.

Introduction

Clomifene citrate has been the first-line medical treatment for polycystic ovarian syndrome-related (WHO class II) infertility for over 30 years. It acts by up-regulating follicle stimulating hormone, which encourages follicular development (Wallach & Adashi, 1984). However, more than one follicle may result, thus increasing the risk of multiple pregnancy from the background rate of 1.6% to approximately 5–8%
(Legro, 2016; Office for National Statistics, 2017). The majority are dichorionic twins, with the risk of triplets reported as 0.3–0.5%, quadruplets 0.3% and quintuplets 0.13% (McDowell, Kroon, & Yazdani, 2013).

It is well established that multiple pregnancies are associated with adverse maternal, fetal and neonatal outcomes. To address this risk, clomifene should be prescribed at the lowest ovulatory dose. The conventional starting dose is 50 mg daily, for 5 days in the follicular phase. Assessment of serum mid-luteal progesterone might then be used to confirm whether ovulation has occurred, allowing a dose increase in the subsequent cycle if not.

The National Institute for Health and Care Excellence (NICE) does not advise the use of mid-luteal progesterone assessment for patients taking clomifene, but gives this guidance (National Institute for Health and Care Excellence, 2013):

> For women who are taking clomifene citrate, offer ultrasound monitoring during at least the first cycle of treatment to ensure that they are taking a dose that minimises the risk of multiple pregnancy. (1.5.2.3, Clinical Guideline 156)

The Royal College of Obstetricians and Gynaecologists has recommended serial ultrasound monitoring for clomifene-associated follicular development since 1998, and NICE adopted the guideline in 2004 (National Institute for Clinical Excellence, 2004; Royal College of Obstetricians and Gynaecologists, 1998). It is based on expert opinion rather than research evidence. A systematic review cast doubt upon the advice, concluding that there is insufficient data to support its use (Galazis, Zertalis, Haoula, & Atiomo, 2011). The rationale for ultrasound monitoring is to detect multifollicular development and enable

1. Which of the following best describes your role?
   - ⓿ Consultant Obstetrician/Gynaecologist
   - ⓿ Specialty trainee (ST3 or above)
   - ⓿ Specialty trainee (ST1-ST2)
   - ⓿ Staff grade or associate specialist
   - ⓿ Trainee doctor in specialty other than O&G
   - ⓿ Specialist nurse
   - ⓿ Other (please specify)
2. Do you work with NHS patients or in the private sector?
   - ⓿ NHS only
   - ⓿ Private sector only
   - ⓿ Both NHS and private (Please answer the rest of the survey in relation to your NHS work)
3. In which settings do you prescribe clomifene?
   - ⓿ In a dedicated fertility service WITH immediate access to ultrasound
   - ⓿ In a dedicated fertility service WITHOUT immediate access to ultrasound
   - ⓿ In a general gynaecology outpatient clinic
   - ⓿ In a community-based gynaecology service
4. In an average month, how many first-cycle clomifene prescriptions do you issue?
5. In the routine management of NHS patients taking their first cycle of clomifene, how often would you arrange:
   - 5.1 An ultrasound scan for multifollicular development (i.e. for multiple pregnancy risk)?
   - 5.2 Serum mid-luteal progesterone level as a marker of ovulation?

   Options: never, rarely, occasionally, sometimes, frequently, usually, always
6. What are your thoughts about monitoring for multiple pregnancy risk after clomifene use?
   NICE advises the use of TVUS during the first cycle of treatment. Do you have any thoughts regarding this?
7. Do you have local guidelines regarding first-cycle clomifene use?
   If yes, are you aware of the content of local guidelines regarding monitoring? What would be considered a significant ultrasound finding in terms of multiple pregnancy risk?
8. Please indicate the conditions for which you would prescribe clomifene
   - ⓿ Unexplained infertility
   - ⓿ Ovulatory disorders
   - ⓿ Tubal damage
   - ⓿ Male factors

Figure 1. Questions from the paper-based survey.

the clinician to advise abstinence from intercourse during an affected cycle. Opponents argue that monitoring is expensive, cannot prevent intercourse in women who have multifollicular development, and that evidence of improved outcomes is lacking. The guideline also limits clomifene use to settings where timely transvaginal ultrasonography (TVUS) is available, hence it is now rarely prescribed in primary care (OpenPrescribing.net, 2018; Wilkes, Chinn, Murdoch, & Rubin, 2009).

Anecdotal evidence suggests that the NICE guideline for TVUS is not always followed. To investigate this contentious issue further, we conducted a survey of UK-based consultant gynaecologists and fertility specialists.

Materials and methods

Participants

The target sample population was UK-based consultant gynaecologists and fertility specialists who currently prescribe clomifene for ovulatory disorders.

Survey design

The online survey was developed using SurveyMonkey (www.surveymonkey.com). The primary outcome data related to the likelihood of using TVUS during the first cycle of clomifene therapy. For simplicity, respondents working in both the NHS and the private sector were asked to relate their answers to NHS work only. The survey was piloted with two experts in reproductive medicine, and minor adjustments made (Figure 1).

Distribution

Publicly available professional email addresses were found by searching online. A link to the online survey was sent to 893 consultant gynaecologists in April 2017, followed by a reminder email after three weeks.. The link was also published in the British Fertility Society (BFS) newsletter, and by Fertility Network UK via twitter. A comparable postal survey was sent to the Clinical Director of each of the 86 Human

Fertilisation and Embryology Authority (HFEA)-licenced fertility units in the UK, and the Clinical Director for Gynaecology in each of the 140 NHS trusts providing gynaecology services in England. The postal survey was distributed on 28 July 2017. The postal and online surveys remained open until 07 September 2017. All responses were anonymous.

Analysis

A concurrent triangulation strategy was used comprising cross-validation of quantitative data with qualitative findings (Cresswell & Plano-Clark, 2003). Nominal,

Table 1. Proportion of respondents stating their routine use of TVUS for multiple pregnancy risk, and/or serum mid-luteal progesterone as a marker of ovulation.

Frequency of use	TVUS	Serum mid-luteal progesterone
Never	24 (21.8%)	9 (8.3%)
Rarely	11 (10.0%)	4 (3.7%)
Occasionally	4 (3.6%)	8 (7.3%)
Sometimes	8 (7.3%)	4 (3.7%)
Frequently	4 (3.6%)	4 (3.7%)
Usually	5 (4.5%)	16 (14.7%)
Always	54 (49.1%)	64 (58.7%)
Total number of respondents	110	109

discrete and ordinal data were processed in SPSS (Statistical Package for Social Sciences, version 24.0). Frequencies and ordinal labels were converted to percentages with 95% confidence intervals (CI) where appropriate. Spearman's rho correlation was applied to look for a relationship between the use of the two monitoring methods. Comparative analysis was completed using the Pearson v^2 test and Cramer's V. A pvalue <0.05 was considered significant. Frequency categories were grouped so that at least 20% of cell counts were over the expected cell value. Where data were missing, the denominator was reduced to the number of respondents.

Free text answers were transported into NVivo Pro (version 11.4) for qualitative data analysis using a framework thematic approach. Once the survey was closed, qualitative responses were categorized into core themes by HG. A thematic framework was developed based on a priori issues and emergent in vivo issues to help ensure credibility. Themes were independently reviewed by KK. The framework was applied to the dataset, and a detailed index of data was created. This was then refined and related to give a descriptive and explanatory account of the whole dataset in concurrence with the quantitative findings.

Ethical approval

Ethical consent was obtained from the University of Sunderland Research Ethics Committee (000392). NHS ethics approval was not required (http://www.hra-decisiontools.org.uk/ethics/).

Results

Response rate

Of the initial round of email invitations to the online survey, 219 (24.5%) were opened and 19 (2.1%) complete surveys were submitted. Another 40 were submitted following the second round of emails and endorsement by the BFS and Fertility Network UK; the unknown denominator population prevents us from reporting the response rate. Of the postal surveys, 70 (31.0%) were completed and returned.

A total of 129 completed surveys were returned. Of these, 19 (14.7%) were excluded because they were not completed by consultants currently prescribing clomifene, or because key data was missing.
Therefore, 110 surveys were included in analysis.

Respondent characteristics

A total of 96 respondents (87.3%) were NHS employees and 14 (12.7%) worked in the private sector only. Overall, 74 (67.3%) were prescribing clomifene in a dedicated fertility service with immediate access to TVUS. Responses came from a wide geographical spread across the UK.

Key findings

Of 110 respondents, 54 (49.1%) were always using TVUS to monitor first-cycle clomifene (Table 1), therefore 56 respondents (50.9%) were not always practicing in accordance with NICE Clinical Guideline 156 (95% CI 41.56–60.24%). The overall frequency of TVUS monitoring during first-cycle clomifene was 61.45% (95% CI 53.26–69.64%).

Clinicians working in a fertility service with immediate access to ultrasound were significantly more likely to always scan than those working in a fertility service without immediate access (47/66 versus 1/11; v^2 14.62; df 1; $p < 0.01$; Cramer's V 0.427; Table 2). A significant difference was also seen when responses from gynaecology outpatient clinics and community gynaecology were added to the group without immediate ultrasound access (47/66 versus 5/33; v^2 27.73; df 1; $p < 0.01$; Cramer's V 0.529). There was no significant difference in the management of NHS and private patients (48/96 versus 6/14; v^2 0.25; df 1; p ¼ 0.62).

Of 108 responses, 66 (61.1%) said that they have local guidelines, and 28 gave further details. All guidelines classed a finding of either three or four follicles significant. The follicular size considered significant was either not given, or ranged from 12 to 20 mm (n ¼ 19, mean 15.5 mm). Other local guidelines suggested that follicles should be 'mature' or a
'good size'.

When asked about the use of serum mid-luteal progesterone, 80 respondents (73.4%) said that they request it either usually (n ¼ 16) or always (n ¼ 64). There was a weak negative correlation between the use of ultrasound and serum mid-luteal progesterone

Table 2. Implications of accessibility on the frequency of TVUS use following first-cycle clomifene.

Frequency of use	Fertility service with immediate access to TVUS	Fertility service without immediate access to TVUS	Gynaecology outpatient or community clinic	Total
Never	6 (9.1%)	5 (45.5%)	11 (50.0%)	22
Rarely	3 (4.5%)	5 (45.5%)	1 (4.5%)	9
Occasionally	1 (1.5%)	–	2 (9.0%)	3
Sometimes	3 (4.5%)	–	3 (13.6%)	6
Frequently	2 (3.0%)	–	1 (4.5%)	3
Usually	4 (6.0%)	–	–	4
Always	47 (71.2%)	1 (9.0%)	4 (18.2%)	52
Total	66	11	22	99

Significant difference seen in practice depending on access to TVUS (v^2 27.73; df 1; p< 0.01; Cramer's V 0.529). Chi-square assumes equal distribution of practice for each setting type (null hypothesis); this also assumes that the guideline has no influence on practice. Smaller sample size accounts for non-response or clinicians who prescribe in more than one setting and were therefore discounted from this analysis.

(Spearman's rho correlation 0.24; p ¼ 0.012; two-sided).

All respondents said that they prescribe clomifene for ovulatory disorders; 25 respondents (22.7%) indicated that they also use it for unexplained infertility.

Qualitative data analysis

Five key themes arose from free text responses: (i) using personal experience to justify practice, (ii) impact of resource availability, (iii) consideration of the evidence base, (iv) justification for scanning the first cycle only, and (v) accepting a risk of multiple pregnancy.

Theme 1: using personal experience to justify practice

Sixteen respondents specifically referred to their own experience. Three used their experience to justify their use of TVUS, while eleven referred to experience to justify practice that was not concordant with the guidelines; they never or rarely scanned first-cycle clomifene patients and described low or zero rates of multiple pregnancy over decades of prescribing:

> [Scanning] is a waste of time and often erroneous. The appearance of ovaries after clomifene exposure often looks dramatic and cycles can be cancelled unnecessarily …
>
> Respondent number: 12 (never scans)

Theme 2: impact of resource availability

Limited resource availability was the most commonly occurring theme, with 22 respondents referring to lack of facilities, capacity or funding:

> The massive issue is the resources. NICE is good for giving guidelines but ground reality is very different. Even if it is ideal unfortunately it is not possible to scan them even once. Respondent number: 109
> (never scans)

Theme 3: consideration of the evidence base

Four respondents referred to the lack of evidence base for NICE Clinical Guideline 156:

> Although we offer U/S in 1st cycle, there is no strong evidence that this reduces risk of multiple pregnancies. You need to consider cost, time wasted for patients/staff, and anxiety for patient. Respondent number: 116 (always scans)

Theme 4: justification for scanning the first cycle only

There were 22 responses relating to this issue. One respondent said that scanning the first cycle only is appropriate, while 21 expressed concern. Eight respondents said that they scan every clomifeneinduced cycle. Six were scanning in the first cycle and following dose changes; two were scanning every cycle only when other risk factors for multiple pregnancy were present; and two were scanning only when high doses were used:

> Disagree with this advice [to only scan the first cycle], as multifollicular development could occur in subsequent ovulation induction cycles, although the risk of multiple pregnancy is low. Respondent number:
> 91 (always scans)

Theme 5: accepting a risk of multiple pregnancy

Respondents who were not routinely scanning often described the need to make the patient aware of the risks of multiple pregnancy:

A risk of multiple pregnancy of 8-10% discussed at consultation. This is agreed and accepted by pt before prescription. Respondent number: 37 (never scans)

Discussion

In this study, over half of the clinicians surveyed were not always using TVUS to monitor clomifene-associated multiple pregnancy risk, and their practice is therefore contrary to NICE Clinical Guideline 156. The main reasons cited for this were resource limitations, personal experience of low multiple pregnancy rates and the lack of an evidence base. The survey also suggested that clinicians and patients are often willing to accept a risk of multiple pregnancy with clomifene. The relevance of scanning the first cycle only was brought into question. Interestingly, 22.9% of respondents indicated that they use clomifene for unexplained infertility, despite evidence that it is no more effective than expectant management (Bhattacharya et al., 2008; Hughes, Brown, Collins, & Vanderkerchove, 2010). Further analysis regarding this is beyond the scope of this paper.

To our knowledge, this is the first study investigating compliance with NICE regarding first-cycle TVUS monitoring during clomifene therapy. The survey collected responses from across the UK, from senior clinicians making treatment decisions. The main limitations arise from recruitment difficulties and a low-level response rate. Email invitations possibly remained unopened due to invalid addresses, rejection of an unknown sender domain or if invitees felt overburdened by emails. The response to the subsequent postal survey was comparable to similar studies in the field (Hackethal et al., 2010; Nandi, Gudi, Shah, & Homburg, 2015). Because of the pragmatic approach to recruitment based on available data, those working solely in the private sector were represented by a small sample, affecting the applicability of comparative analysis. Non-response analysis was not possible due to the limited demographic data collected; however, bias may be low due to the relative within-group homogeneity of the study sample (Flanigan, McFarlane, & Cook, 2008; Kellerman & Herold, 2001). Free text answers helped to explain the quantitative outcomes and added to the credibility of the data.

In one previous study, the incidence of multifollicular development (defined as three or more follicles 14 mm) was reported as 17% in normo-ovulatory women and 6% in the ovulatory dysfunction group, resulting in 56 of 425 cycles (13.2%) being cancelled (Coughlan, Fitzgerald, Milne, & Wingfield, 2010). All the reported multiple pregnancies occurred with unifollicular development, while TVUS evidence of multiple follicles did not necessarily correlate with multiple pregnancy.

NICE gives no specific indication regarding the size or number or follicles that should be considered significant when scanning. Our survey found that the lowest cut-off follicular diameter quoted in local guidelines was 12 mm. Dickey and Holtkamp (1996) advised that all follicles down to 10 mm diameter should be considered when monitoring multiple pregnancy risk. They also reported that while the average number 12 mm diameter seen each cycle is 2.3, the optimum response to treatment is seen with at least four follicles. According to local guidelines quoted in the survey responses, a finding of three or four follicles would prompt advice to the patient to abstain from intercourse, therefore possibly denying them the optimum treatment effect.

NICE does suggest scanning in the first cycle of clomifene only, assuming that women are at the greatest risk of overstimulation when first exposed to the medication. The relevance of scanning the first cycle to ensure safety in subsequent cycles is not well researched or understood. There can be a cumulative effect of clomifene from one cycle to the next, given its half-life of 5–7 days (Mikkelson et al., 1986; Weller, Daniel, Koren, Lunenfeld, & Levy, 2017), and women can have significantly different responses between cycles (Coughlan et al., 2010). There can also be inconsistent responses to a particular dose between patients, suggesting that follicular development cannot be safely predicted based on a first-cycle scan.

Cost effectiveness has not been formally assessed regarding clomifene monitoring with TVUS. Resource limitations and access to TVUS are having a significant impact on the management of patients taking clomifene, based on their location. However, 33.8% of clinicians surveyed who have immediate access to TVUS are not always using it, suggesting that factors other than resources contribute to non-adherence with this guideline.

Serum mid-luteal progesterone levels provide a reliable indicator of ovulation where it has occurred but give no information about multiple pregnancy risk. In a study where 75.3% of participants received clomifene, monitoring cycles using progesterone levels only was found to be effective with a multiple pregnancy rate of 4.6% (Stanford, Parnell, & Boyle, 2008). We saw a weak negative correlation between TVUS and serum progesterone use, which may be partly explained by the high number of respondents checking progesterone levels regardless of their TVUS use. However, of the 24 respondents who stated that they never scan, 21 were

always using serum mid-luteal progesterone levels. A blood test may therefore be considered a viable alternative by clinicians who opt not to scan.

In conclusion, the diverse responses to our survey indicate a continued clinical uncertainty and variation in practice despite the presence of a national guideline. This suggests a need for further evidence. The authors intend to conduct a feasibility cohort study and cost effectiveness analysis to compare outcomes associated with TVUS versus serum midluteal progesterone monitoring during clomifene therapy. If serum mid-luteal progesterone monitoring is shown to be at least equivalent to first-cycle TVUS monitoring of clomifene, this will likely challenge the need for invasive testing, and potentially reduce unnecessary cycle cancellations and subsequent progression to IVF. Conversely, if TVUS during first-cycle treatment is found to be appropriate, an evidence base will be available to reinforce the current national guideline.

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Disclosure of interest

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