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REVIEW

The management of unexplained infertility: an evidence-based guideline from the Canadian Fertility and Andrology Society

BIOGRAPHY

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KEY MESSAGE

Unexplained infertility is a common problem and remains a diagnosis of exclusion. There is a role for less invasive treatment options such as expectant management and intrauterine insemination. Advancing to IVF improves live birth rates per cycle and reduces multiple pregnancy, although it is invasive and costly.

ABSTRACT

Unexplained infertility is a common diagnosis affecting as many as 50% of couples seeking infertility care. As a diagnosis of exclusion, its treatment remains largely empirical. Historically, a step-wise progression in treatment has been initiated with the least invasive, least expensive option followed by a gradual progression to therapies using assisted reproductive technology. In recent years there have been advocates for more rapid-progression IVF. This guideline from the Canadian Fertility and Andrology Society (CFAS) provides comprehensive, evidence-based recommendations for the treatment of unexplained infertility, including expectant management, laparoscopy, intrauterine insemination (IUI) alone, ovarian stimulation with oral agents or gonadotropins alone, ovarian stimulation + IUI, and IVF. The quality of supporting evidence for each recommendation is evaluated using the framework outlined by the Canadian Task Force on Preventive Health Care. This guideline recognizes that the therapeutic approach should be individualized taking into account patient age and duration of infertility, and emphasizes those strategies that are most likely to result in a healthy live birth.

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KEYWORDS

Evidence-based management
Expectant management
IVF
Intrauterine insemination (IUI)
Unexplained infertility

INTRODUCTION

Infertility is defined as the failure to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse (*Zegers-Hochschild et al., 2017*). Unexplained infertility (UEI) is defined as the absence of identifiable causes for the infertility (*Moghissi and Wallach, 1983; Zegers-Hochschild et al., 2017*). However, the diagnostic testing required to meet the definition of UEI that is most commonly described in the literature is based only on the presence of normal ovulatory function, a normal semen analysis and at least one patent Fallopian tube (*Crosignani et al., 1993*). It is estimated that 30–50% of couples presenting for the evaluation of infertility have UEI based on these simple criteria (*Collins and Crosignani, 1992; Esteves et al., 2015*).

In clinical practice, however, we recognize the limitations of this diagnostic evaluation. Age, ovarian reserve, oocyte quality, endometriosis, uterine factors, cervical mucus factors, tubal dysfunction, immunological factors, genetic factors, coital difficulties, other male factors and failed fertilization may all contribute to infertility. These factors are not necessarily excluded in the majority of published studies of UEI.

Natural per cycle conception rates decline as the number of failed attempts at conception increases. In young couples (female age 23–37 years) who have not previously attempted to conceive, the pregnancy rate per month is 30% in the first 2 months, but declines to 8% after 6 months and 4% after 9–12 months (*Zinaman et al., 1996*). However, cumulative pregnancy rates even with low monthly conception rates can be encouraging (TABLE 1).

Female age has an important impact on fecundity rates. Female age is a strong predictor of both natural and treatment-related live birth rates, with rates decreasing after 35 years of age (*Kamel, 2010*).

The management of UEI is typically empirical, with consideration of the efficacy, safety, cost and risks of each treatment option. Historically, a step-wise progression in treatment has been initiated, with the least invasive, least expensive option followed by a gradual progression to assisted reproductive therapies if the initial treatments fail. Some recent practice has advocated moving more quickly to therapies using assisted reproductive technology (*Reindollar et al., 2010*).

The aim of this guideline is to provide evidence-based recommendations on the management of UEI including expectant management, surgical intervention (laparoscopy), intrauterine insemination (IUI), ovarian stimulation with oral agents or gonadotropins, and IVF with and without intracytoplasmic sperm injection (ICSI). The quality of supporting evidence and clinical recommendations were evaluated using the framework developed by the Canadian Task Force on Preventive Health Care (*Canadian Task Force on Preventive Health Care, 2003*) (TABLE 2).

EXPECTANT MANAGEMENT OF UEI

Expectant management has long been an option in the management of UEI and there is evidence to suggest it as an effective approach in good-prognosis couples. Retrospective data have shown a cumulative pregnancy rate over 2 years as high as 72% in young women, with a decline to 45% in women aged over 35, and further to 30% in couples with more than 5 years of infertility (*Hull et al., 1985*). Although only two randomized controlled clinical trials (RCT) of couples with a good prognosis have evaluated expectant management, both trials demonstrated reasonable live birth rates.

Steures and colleagues (*Steures et al., 2006*) published a multicentre trial of 253 good-prognosis couples (mean age 33 years, median duration of infertility 2 years): 127 were assigned to immediate treatment and 126 to expectant management. The authors found a 27% probability of live birth without intervention after 6 months. Expectant management did not demonstrate a delay in time to conception compared with the immediate treatment group. Bhattacharya and co-workers (*Bhattacharya et al. 2008*) published an RCT of 580 couples (mean age 32 years, median duration of infertility 2.5 years); the trial had three arms: 193 couples were randomized to expectant management, 194 to oral clomiphene citrate alone, and 193 to unstimulated IUI (n = 193) for 6 months. In the expectant management group, the live birth rate after 6 months was 32/193 (17%), compared with 26/192 (14%) in the clomiphene citrate group and 43/191

TABLE 1 CUMULATIVE PROBABILITY OF AN OUTCOME BASED ON A STABLE MONTHLY RATE

Monthly chance (%)	After 2 months (%)	After 3 months (%)	After 4 months (%)	After 6 months (%)	After 9 months (%)	After 12 months (%)	After 24 months (%)
40	64	78	87	95			
30	51	66	76	88			
20	36	49	59	74	87		
15	28	39	48	62	77	86	98
10	19	27	34	47	61	72	92
8	15	22	28	39	53	63	86
6	12	17	22	27	43	52	77
5	10	14	19	26	37	46	71
4	8	12	15	22	31	39	62
3	6	9	11	17	24	31	52
2	4	6	8	11	17	22	38
1	2	3	4	6	9	11	21

TABLE 2 QUALITY OF EVIDENCE ASSESSMENT AND CLASSIFICATION OF RECOMMENDATIONS AS DEFINED BY THE CANADIAN TASK FORCE ON PREVENTIVE HEALTH CARE

Quality of evidence assessment		Recommendations	
I	Evidence obtained from a least one properly randomized controlled trial	A	There is good evidence to recommend the clinical preventive action
II-1	Evidence from well-designed controlled trials without randomization	B	There is fair evidence to recommend the clinical preventive action
II-2	Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C	The existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3	Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D	There is fair evidence to recommend against the clinical preventive action
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E	There is good evidence to recommend against the clinical preventive action
		L	There is insufficient evidence (in quantity and/or quality) to make a recommendation; however, other factors may influence decision-making

(23%) in the IUI group. None of these differences was significantly different.

Patient experience was surveyed in both these studies. Steures and colleagues' study reported a positive patient experience with expectant management, but Bhattacharya and colleagues reported that a greater proportion of women randomized to the treatment groups than to expectant management found the process of management over the 6 months more acceptable.

Recommendation:

1. In couples with a good prognosis (based on age and duration of infertility) expectant management can be offered (Level 1A).

LAPAROSCOPIC SURGERY IN UEI

The recommendations of the American Society for Reproductive Medicine committee for the evaluation of female infertility (*American Society for Reproductive Medicine, 2015*) suggest that, in the absence of evidence of tubal or other pelvic pathology on initial less invasive investigations (namely hysterosonography or pelvic ultrasound), laparoscopy is not warranted in the diagnostic work-up of infertility, nor is it needed to diagnose UEI, although the recommendations concede that there may be a place for diagnostic laparoscopy in young women with a long period (over 3 years) of infertility but no recognized abnormalities.

Two RCT have compared laparoscopic ablation or excision and adhesiolysis of endometriotic lesions versus diagnostic laparoscopy alone in stage I–II endometriosis. In the EndoCan study, 717 women (aged 20–39 years) with UEI underwent laparoscopy and 341 had minimal or mild endometriosis (*Marcoux et al., 1997*). The cumulative ongoing pregnancy rate was 31% in the non-blinded, surgically treated group and 18% in the non-blinded, surgically untreated, laparoscopy-only group. The monthly fecundity rate was 4.7% in the treated arm and 2.4% in the untreated arm. A follow-up analysis of the 263 women enrolled in EndoCan who underwent laparoscopy but who did not have endometriosis and who were managed expectantly reported a monthly fecundity rate of 3.5% (*Berube et al., 1998*), almost precisely between the monthly rate of women who were informed that they had untreated endometriosis, and the rate of women who were informed that their endometriosis had been treated.

In the Gruppo Italiano study (*Parazzini, 1999*), 101 women (aged under 36 years) with minimal or mild endometriosis were randomized at laparoscopy, 54 to surgical treatment and 47 to no surgical treatment. The live birth rate after 12 months was 19.6% in the treated group and 19.6% in the untreated group. A bias may have been introduced in this study by the large number of patients who took gonadotropin-releasing hormone agonists after surgery.

With both studies combined, the number needed to treat (NNT) is 12, although with a prevalence of minimal/mild endometriosis in UEI of 40–50% the NNT would be likely to be increased.

Recommendation:

2. In the absence of evidence for tubal or other pelvic pathology, laparoscopy is not warranted in UEI (Level II-2B).

IUI ALONE (NATURAL-CYCLE IUI)

The largest study assessing the benefit of IUI alone in UEI involved over 900 couples who were randomized to intracervical insemination (ICI) alone, IUI alone, gonadotropins + ICI, or gonadotropins + IUI for up to four cycles (*Guzick et al., 1999*). In 234 women (mean age 32 years, duration of infertility 3.8 years) IUI alone resulted in a 5% chance of conception per cycle and an 18% chance of pregnancy per couple.

In the only RCT examining IUI alone versus expectant management (average age 32 years, duration of infertility 2.5 years), no significant difference was found in the cumulative live birth rates of 16% after 6 months expectant management and 23% in the IUI-alone group ($P = 0.11$) (*Bhattacharya et al., 2008*). This is the only RCT comparing these two groups in the Cochrane IUI review (*Veltman-Velhurst et al., 2016*).

Recommendation:

3. Natural-cycle IUI does not offer any benefit over expectant management and should not be offered in UEI (Level 1A).

OVARIAN STIMULATION WITH ORAL AGENTS ALONE

In 2010 a Cochrane review of the literature was published to determine the effectiveness of clomiphene citrate in improving pregnancy outcomes in women with UEI (*Hughes et al., 2010*), pooling data from 1159 participants in seven trials. There was no evidence that clomiphene citrate was more effective than no treatment on the live birth rate

(odds ratio [OR] 0.79, 95% confidence interval [CI] 0.45–1.28).

Aromatase inhibitors, such as letrozole, have also been used extensively in couples with UEI. A systemic review (*Liu et al., 2014*) compared the use of letrozole alone and clomiphene citrate alone in UEI. It included data from three studies (*Al-Fozan et al., 2004; Badawy et al., 2009; Ibrahim et al., 2012*) with a total of 1776 women reporting on clinical pregnancy. Letrozole use was associated with a pregnancy rate of 199/809 (24.5%) in randomized trials, while the use of clomiphene citrate was associated with a pregnancy rate of 201/967 (20.8%). The difference was not statistically significant (Relative Risk (RR) 1.26, 95% CI 0.89–1.80), although one of the included studies (*Badawy et al., 2009*) also used IUI.

There was no statistically significant difference in the rate of multiple pregnancies with respect to letrozole (8/195, 4.1%) or clomiphene citrate (16/200, 8.0%) and there was no difference in any other adverse events.

Recommendations:

4. Clomiphene citrate alone does not offer any benefit over expectant management and should not be offered to couples with UEI (Level 1A).
5. Aromatase inhibitors alone do not offer any benefit in comparison to clomiphene citrate alone and should not be offered to couples with UEI (Level 1A).

OVARIAN STIMULATION WITH GONADOTROPINS ALONE

The use of superovulation with gonadotropins as an empirical treatment for UEI became popular in the 1980s and 1990s based on the hypothesis that increasing the number of oocytes available for fertilization would increase the clinical pregnancy and live birth rates.

While gonadotropin ovarian stimulation (gonadotropin-OS) alone may offer benefit in the treatment of UEI, it is associated with a high risk of multiple pregnancy (*Gleicher et al., 2000*). Over the past two decades, there have been minimal published data concerning the use of gonadotropin-OS alone in UEI, and there are no RCT comparing ovarian stimulation with gonadotropins and expectant management.

Recommendation:

6. There is insufficient evidence to recommend gonadotropin-OS alone in the management of UEI (Level IIIL).

OVARIAN STIMULATION WITH ORAL AGENTS AND IUI

Several prospective studies have evaluated ovarian stimulation with oral agents and IUI. Only two have compared oral agents and IUI with expectant management. A historic small study (*Deaton et al., 1990*), compared clomiphene citrate/IUI with expectant management. In this study, 24 patients had UEI and 27 patients had surgically corrected endometriosis (mean age 33 years, duration of infertility 3.5 years). The pregnancy rate per cycle was 9.4% in the clomiphene citrate/IUI group and 3.3% in the expectant management group. More recently, Farquhar and colleagues (*Farquhar et al., 2018*) compared 101 women randomized to undergo up to three cycles of IUI with oral agents (principally clomiphene citrate, although seven received letrozole) with 100 women randomized to 3 months expectant management (mean age 34 years, duration of infertility 3.6 years). The cumulative live birth rate in the oral agent and IUI group was 31% and the live birth rate in the expectant management group was 9%.

Two RCT have compared clomiphene citrate/IUI with letrozole/IUI. A trial of 214 UEI couples (mean age 26 years, duration of infertility 3.5 years) showed a clinical pregnancy rate per cycle of 18% with letrozole/IUI and 11% with clomiphene citrate/IUI (*Fouda and Sayed, 2011*). The other RCT (*Badawy et al., 2009*) randomized 412 couples (mean age 29 years, duration of infertility longer than 1 year). The cumulative pregnancy rate was 37% with letrozole/IUI and 36% with clomiphene citrate/IUI. The per-cycle pregnancy rate was 19.0% and 18.3%, respectively.

The largest RCT comparing clomiphene citrate/IUI with letrozole/IUI (and gonadotropin/IUI) is the multicentre Assessment of Multiple Intrauterine Gestations From Ovarian Stimulation (AMIGOS) trial (*Diamond et al., 2015a, 2015b*). In this study, 900 patients (mean age 32 years, duration of infertility 2.9 years) were randomized to one of three treatment arms for a total of four cycles: (i) letrozole/IUI; (ii) clomiphene citrate/IUI; and (iii) FSH/IUI. The cumulative live birth rate was 23.3% with clomiphene citrate/IUI and 18.7% with letrozole/IUI, but the difference was not statistically significant. Per-cycle pregnancy rates were 9.6% and 7.3%, respectively. Multiple pregnancy rates were 13% with letrozole/IUI and 9% with clomiphene citrate/IUI.

Given the ease, cost and lower rate of multiple pregnancy, IUI with oral agents is a standard first-line therapy in good-prognosis women with UEI.

Recommendations:

7. IUI with oral agents is an appropriate treatment in couples with UEI and is more effective than expectant management (Level IA).
8. Either letrozole or clomiphene citrate can be used for IUI with oral agents (Level 1A).

OVARIAN STIMULATION WITH GONADOTROPINS AND IUI

Numerous RCT have evaluated the use of IUI and ovarian stimulation with gonadotropins in couples with UEI.

Gonadotropin/IUI versus gonadotropin alone

Several prospective studies have compared gonadotropin/IUI with gonadotropin alone and have been reviewed in the recent Cochrane review on the use of IUI in UEI (*Veltman-Verhulst et al., 2016*). The pooled data included a total of 231 couples in the gonadotropin/IUI arms and 246 couples in the gonadotropin alone arms and demonstrated that gonadotropin/IUI is associated with a higher pregnancy rate per couple (OR 1.69, 95% CI 1.14–2.53) compared with gonadotropin alone.

Multiple pregnancy rates when reported ranged from 5% to 12%, and there was no difference in multiple pregnancy rates between gonadotropin/IUI and gonadotropins alone.

Gonadotropin/IUI versus clomiphene citrate/IUI

Three RCT have compared gonadotropin/IUI and clomiphene citrate/IUI. Two smaller studies compared clomiphene citrate/IUI with gonadotropin/IUI (*Berker et al., 2011; Dankert et al., 2007*), and the AMIGOS

trial compared clomiphene citrate/IUI, letrozole/IUI and gonadotropin/IUI (*Diamond et al., 2015a*).

The smaller RCT comparing clomiphene citrate/IUI with gonadotropin/IUI randomized 93 couples and 68 couples with UEI, respectively. Ongoing pregnancy rates per cycle were 11.6% with clomiphene citrate/IUI and 18% with gonadotropin/IUI in the first trial. In the second trial after four cycles, the cumulative live birth rate was 31.4% and 30.3%, respectively, although there was a higher cancellation rate primarily for over-response in the gonadotropin/IUI group, and the multiple pregnancy rate was lower (4.3%) than with clomiphene citrate/IUI (7.4%).

The AMIGOS trial compared 300 women undergoing up to four cycles of clomiphene citrate/IUI (starting at 100 mg) with 301 women undergoing up to four cycles gonadotropin/IUI (starting at 150 IU Menopur). Cycles were cancelled if there were more than four mature follicles on the day of human chorionic gonadotropin administration. The cumulative live birth rate was 32.2% with gonadotropin/IUI and 23.3% with clomiphene citrate/IUI. The multiple gestation rate was 31.8% with gonadotropin/IUI (24 twins and 10 triplets) and 9.4% with clomiphene citrate/IUI (eight twins and no triplets).

Gonadotropin/IUI versus letrozole/IUI

Two smaller studies compared letrozole/IUI with gonadotropin/IUI. The first (*Baysoy et al., 2006*) randomized 78 couples (mean age 28 years, duration of infertility 5.7 years) undergoing a first IUI cycle to either letrozole/IUI or human menopausal gonadotropin/IUI (75 or 150 IU; dose based on age) followed by IUI. The clinical pregnancy rate was 18.4% for the letrozole/IUI group and 15.7% for gonadotropin/IUI. The second study (*Gregoriou et al., 2008*) randomized 50 couples (mean age 32 years, duration of infertility 3.8 years) who had previously failed three cycles of clomiphene citrate/IUI to receive either FSH/IUI (150 IU) or letrozole/IUI for a maximum of three cycles. The cumulative live birth rate was 36% for the gonadotropin/IUI group and 24% for the letrozole/IUI group. The live birth rate/cycle was 10.9% in the gonadotropin/IUI group and 7.5% with letrozole/IUI, and no multiple gestations were reported in either group.

The AMIGOS trial (*Diamond et al., 2015a*) reported a live birth rate of 32.2% with gonadotropin/IUI and 18.7% with letrozole/IUI. The letrozole group had nine twin pregnancies and no triplets, compared with 24 twins and 10 triplets with gonadotropin/IUI.

The data presented here show that gonadotropin/IUI, particularly when starting at higher doses, is associated with a higher live birth rate than either clomiphene citrate/IUI or letrozole/IUI. However, this higher live birth rate correlates with the increased multiple pregnancy rate associated with gonadotropin/IUI. In studies where there is little difference in the multiple pregnancy rate, the live birth rates or clinical pregnancy rates are similar.

Summary statement:

In gonadotropin/IUI, a higher gonadotropin dose is associated with a higher multiple pregnancy rate and a higher live birth rate (Level II-2A).

Recommendations:

9. Gonadotropin/IUI can be offered to couples with UEI (Level IB).
10. Patients should be aware that gonadotropin/IUI is associated with a higher pregnancy rate per cycle and a higher multiple pregnancy rate per cycle than IUI with oral agents (Level IA).

IVF FOR UEI

IVF has long been accepted as effective treatment for UEI, and international guidelines have recommended IVF in the treatment of UEI (*NICE, 2004, 2013*), although this may not be an option for all couples given the cost and burden of treatment. A 2012 Cochrane systemic Review (*Pandian et al., 2012*) has compared IVF with other treatments for UEI. In that review, one study compared IVF with expectant management (*Hughes et al., 2004*). Fifty-one couples (mean age 32 years, duration of infertility 4.7 years) were randomly allocated to one single IVF cycle within 90 days of randomization or expectant management for a period of 90 days. The live birth rate was 45.8% with IVF and 3.7% with expectant management (OR 22, 95% CI 2.56–189.38). That review also included one trial comparing IVF with IUI alone (natural-cycle IUI) over six cycles (*Goverde et al., 2000*). In this study, in good-prognosis couples, the per cycle pregnancy rate was higher in IVF (12.2%) than IUI alone (7.8%).

Six RCT have compared IVF with gonadotropin/IUI (*Bensdorp et al., 2015; Goldman et al., 2014; Goverde et al., 2000; Nandi et al., 2017; Reindollar et al., 2010; van Rumste et al., 2014*). (TABLE 3). These were a heterogeneous group of studies in terms of study population, treatments and duration of treatment, so pooling of the data was not possible. Goverde and colleagues compared six cycles of gonadotropin/IUI with IVF (as well as the arm with natural-cycle IUI, described above). Reindoller and colleagues examined the rates with clomiphene citrate/IUI in both arms, followed by three cycles of gonadotropin/IUI versus up to six cycles of IVF. Van Rumste and co-workers examined three cycles of gonadotropin/IUI versus one cycle of IVF. Bensdorp and colleagues compared six cycles of ovarian stimulation/IUI with six cycles of IVF in a modified natural cycle with with three cycle of conventional IVF with elective

TABLE 3 PUBLISHED RANDOMIZED CONTROLLED TRIALS COMPARING GONADOTROPIN/IUI WITH IVF FOR THE TREATMENT OF UNEXPLAINED INFERTILITY

Reference	Number of subjects[a]	Clinical pregnancy rate	
		Gonadotropin/IUI	IVF
Goverde et al., 2000	172	7.8% per cycle	12.2% per cycle
Reindollar et al., 2010	503	21.4% after three cycles	52% after three cycles
van Rumste et al., 2014	116	17.2% after three cycles	22.4% per cycle
Bensdorp et al., 2015	602	56.0% after six cycles	58.7% after three cycles
Goldman et al., 2014[b]	154	17.3% after two cycles	49% after two cycles
Nandi et al., 2017	207	28.7% after three cycles	33.1% per cycle

[a] Number of couples randomized to either treatment strategy.

[b] This study specifically assessed couples in which the woman's age was 38–42 years.

IUI, intrauterine insemination.

single-embryo transfer and all subsequent cryo-cycles. Goldman and co-workers compared women aged 38–42 years who were randomized to two cycles of clomiphene citrate/IUI, or two cycles of gonadotropin/IUI, or IVF straight away. Nandi and colleagues compared three cycles of gonadotropin/IUI with one cycle of IVF in treatment-naive couples with UEI.

Although the data are heterogeneous, there is a clear benefit in the live birth rate following IVF over other treatment options in UEI, although adverse events and costs were not analysed.

The Fast Track and Standard Treatment (FASTT) trial (*Reindollar et al., 2010*) demonstrated benefits in terms of mean time to pregnancy (8 months versus 11 months) and cost savings of US$9,800 per delivery with immediate IVF. Nandi and colleagues' study (*Nandi et al., 2017*) also undertook a rudimentary cost analysis and showed similar costs per live birth (£8167 versus £10,560). Neither study assessed the non-treatment costs such as travel for treatment and time away from work.

Given the higher multiple pregnancy rates seen with gonadotropin-COS/IUI, IVF is also seen as offering a benefit in the reduction of multiple pregnancy, a widely accepted adverse event in terms of maternal morbidity and neonatal outcome. The UK national guidelines have advised against gonadotropin/IUI (*NICE, 2004, 2013*) and moving to IVF because of the risk of multiple pregnancy associated with gonadotropin/IUI, which is reduced with elective single-embryo transfer in IVF. The recent Quebec experience also demonstrated that IVF with mandated single-embryo transfer can almost eliminate the risk of multiple births (*Bissonnette et al., 2011*).

However, for many couples with UEI in Canada, the cost of IVF continues to provide a significant barrier to IVF as the first line of treatment, and government funding still falls short for many. Any decision to proceed with IVF should take into account the couple's individual circumstances, particularly with respect to the cost and burden of treatment.

Recommendations:

11. IVF can be offered as an effective first-line treatment in UEI (Level 1B).
12. IVF should be offered to couples with UEI after three cycles of ovarian stimulation/IUI have failed (Level 1A).

ICSI IN UEI

During IVF for UEI, failed fertilization occurs in around 5–10% of cases (*Bungum et al., 2004; Tournaye et al., 2002*). In couples with UEI, adding ICSI could overcome subtle male factor infertility and increase live birth rates. However, RCT comparing conventional IVF with ICSI in non-male factor infertility have not found a benefit for adding ICSI (*Bhattacharya et al., 2001; Bukulmez et al., 2000*).

One small prospective RCT has compared conventional IVF with ICSI in couples with UEI (*Foong et al., 2006*). In this study, 60 patients with UEI (mean age 33 years, duration of infertility 5 years) undergoing one IVF treatment cycle were randomly allocated to conventional IVF or ICSI. The live birth rate was 46.7% with IVF and 50% in the IVF/ICSI group.

A recent systemic review and meta-analysis suggested that routine ICSI was effective in both increasing fertilization rates and decreasing the incidence of total failed fertilization (TFF) (*Johnson et al., 2013*). Although this review included 11 studies published between 1999 and 2011, none of the couples undergoing treatment were randomized. All comparisons related to when individual oocytes were selected for conventional insemination versus ICSI. There was no randomization of oocytes or blinding of the staff; therefore a high risk of potential bias existed. Furthermore, live birth rate was not a reported outcome in any of these studies.

A study examining the cost-effectiveness of splitting oocytes for conventional IVF insemination and for ICSI in a first IVF cycle in couples presenting with UEI found that the minimal increase in live birth rate (3%) did not justify the increased cost of 50:50 IVF:ICSI (*Vitek et al., 2013*), although this was a statistical modelling study.

Rescue ICSI has been advocated in cases of TFF. Pregnancy rates following ICSI in cases of TFF range from 9.7% to 44% and are highest in cases where donor oocytes have been used (*Beck-Fruchter et al., 2014*).

There is still a need for an appropriately powered RCT examining the role of ICSI in UEI.

Recommendation:

13. There is insufficient evidence to recommend the routine addition of ICSI in couples with UEI undergoing IVF to increase the live birth rate, although the addition of ICSI in IVF for UEI may reduce the incidence of TFF (Level 1B).

CONCLUSIONS

UEI, a common problem affecting many Canadian couples, remains a diagnosis of exclusion. In all circumstances the therapeutic approach should involve counselling the couple with regard to expected outcome, adverse events and treatment in terms of the individuality of the couple and their unique history, particularly with regard to age and duration of infertility. There is a role for less invasive treatment options such as expectant management and IUI with ovarian stimulation. An evidence-based approach to the management of UEI suggests a benefit of advancing therapy to IVF in terms of improved live birth rates per cycle and reduced multiple pregnancy, although this approach is invasive and costly.

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