Intrauterine Insemination: An Ineffective Treatment

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13.1 Background

The first paper on intrauterine insemination (IUI) was published by Cohen in the International Journal of Fertility in 1962 [1]. Twenty-five years later, ovarian stimulation and timed IUI was proposed by Dodson et al. for patients with unexplained infertility that had failed other treatment modalities, as a potential alternative to gamete intrafallopian transfer or in vitro fertilization [2]. These authors hypothesized the likelihood of conception would increase by increasing the number of gametes at the site of fertilization [2]. As typically performed, the IUI procedure involves removing the seminal plasma from the ejaculated semen specimen to avoid prostaglandin induced uterine contractions and pelvic infection, concentrating the sperm in culture media to promote capacitation and the acrosome reaction, and finally, dispensing the concentrated sperm into the uterine cavity using a small catheter near the time of ovulation [3]. Since its introduction over 50 years ago, IUI has evolved with changes in sperm preparation and the additions of cycle monitoring and induced ovulation with human chorionic gonadotropin in ovarian stimulation cycles.

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Despite limited evidence of success for any indication, the IUI procedure is commonly utilized in unexplained infertility, mild male factor infertility, minimal-to-mild endometriosis, or as an empirical treatment for a broad range of pro-fertility indications [4]. Because the treatment premise of the IUI procedure is based on increasing the number of gametes at the site of fertilization, most IUI cycles are performed in conjunction with ovulation induction or ovarian hyperstimulation, which are associated with a significant risk of multifetal gestations, which is not effectively controlled by stimulation monitoring. Further, the success of the IUI procedure has remained weak and stagnant, whereas success rates in IVF continue to improve. The discrepancy between successful reproductive outcomes and the risk associated with multifetal gestations will continue to grow between stimulated IUI and IVF as the success rates in IVF continue to improve, particularly as patients and providers continue to increase the utilization of elective single embryo transfer. Finally, the cost analysis data on immediate IVF versus IUI followed by IVF disfavors the initial utilization of unstimulated or stimulated IUI as a cost-effective treatment modality for patients with male factor or unexplained infertility. Herein, we present data to support the argument that IUI should no longer be a standard part of infertility treatment, based on a lack of evidence supporting its efficacy, the risk of adverse events, and cost considerations.

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13.2 IUI Versus Intercourse

Many trials evaluating the efficacy of IUI utilize control populations that undergo timed intercourse (TIC) instead of ordinary intercourse, which may falsely inflate the reported therapeutic benefit of IUI. Timed intercourse dictates that couples abstain from natural coital practices for a period of time prior to the detection of an LH surge, which may reduce the likelihood of pregnancy [4]. This theory is supported by several studies that suggest that the practice of timing the IUI procedure according to the LH surge is appropriate; however, such timing might allow the optimal period for conception via intercourse to pass [4–6]. One study noted that among 221 healthy women attempting conception over 625 menstrual cycles, all recorded pregnancies were associated with intercourse during a 6-day period ending on the day of ovulation (Fig. 13.1) [5]. These authors concluded that chances of conception decline soon after ovulation and that couples abstaining from intercourse until the documentation of the LH surge may miss earlier opportunities for conception [5]. For this reason, we propose that ordinary intercourse, or expectant management, is a more appropriate control in studies of the relative efficacy of IUI. Studies utilizing TIC likely inflate the benefit of IUI and should be interpreted with caution (Fig. 13.1).

13.3 Unstimulated IUI

13.3.1 Cervical Factor Infertility

IUI has been proposed as a specific treatment for cervical hostility, or cervical factor infertility. Although small studies have suggested a benefit for IUI over expectant management in this diagnosis, a statistically significant improvement in ongoing pregnancy rates was not demonstrated [7]. Further, the utility of the postcoital test in defining this phenomenon has been strongly questioned, and a systematic review of five randomized controlled trials found no evidence of efficacy for IUI for this indication [8].

13.3.2 IUI in Male Factor Infertility

IUI has also been suggested as a treatment to overcome male factor infertility as well as to alleviate infertility associated with antisperm antibodies [9]. However, it has been shown that the intrauterine placement of prepared spermatozoa does not alter the frequency of the production of antisperm antibodies in patients undergoing IUI, and it is thus unlikely to treat or prevent infertility associated with this condition [10]. Further, a review that included outcomes for 5,214 IUI cycles from 22 trials concluded that the odds ratio

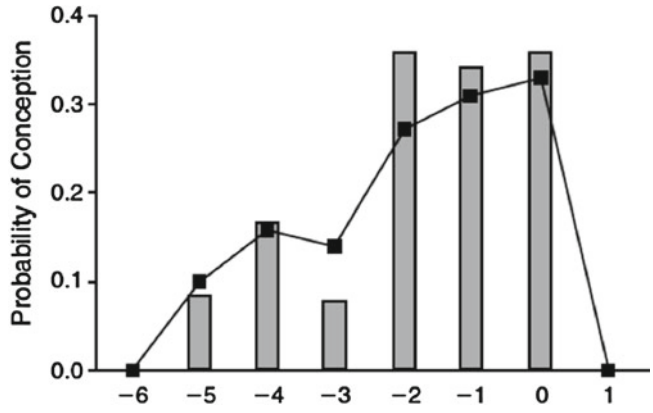

Fig. 13.1 Probability of conception on specific days near the day of ovulation. The *bars* represent probabilities calculated from data on 129 menstrual cycles in which sexual intercourse was recorded to have occurred on only a single day during the 6-day interval ending on the day of ovulation (Day 0). The *solid line* shows daily probabilities based on all 625 cycles, as estimated by the statistical model (Reprinted with permission from Wilcox et al. [5])

for pregnancy was 0.48 [95 % confidence interval (CI), 0.37–0.61] when IUI was performed for male factor, compared to all other diagnoses [11]. Another meta-analysis included data from randomized control trials to assess the efficacy of IUI for male subfertility [12]. These authors reported there was no statistically significant difference when comparing pregnancy rates in IUI versus TIC in natural cycles for male subfertility ($n=21$, OR 5.3, 95 % CI 0.42–67) [12]. The authors concluded that for male subfertility, there was insufficient evidence from randomized control trials to demonstrate improved live birth rates or ongoing pregnancy rates compared to TIC [12]. Since publication of these, an additional crossover study failed to demonstrate a benefit for IUI in natural cycles over TIC in male factor infertility [13].

13.3.3 Unexplained Infertility

IUI has also been proposed as an empiric therapy for unexplained subfertility. However, multiple studies have demonstrated no benefit for this therapy over expectant management. Bhattacharya et al. randomized 580 women with 2 years of unexplained infertility to expectant management, oral CC, or unstimulated IUI for 6 months [14]. They found that compared with expectant management, the odds ratio for a live birth was 1.46 (0.88–2.43) after unstimulated IUI, which was not statistically significant despite a large sample size [14]. Thus, when utilized for male factor or unexplained infertility, the utilization of unstimulated IUI for unexplained infertility or male factor infertility is not currently supported by the literature.

13.4 IUI with Ovarian Stimulation Versus Stimulation Alone

13.4.1 Male Factor Infertility

Data supporting an enhanced pregnancy rate when IUI is added to ovarian stimulation or superovulation is also limited. While a few studies have suggested benefit [15], this has not been supported in a recently published large meta-analysis. Bensdorp et al. evaluated the effectiveness of IUI versus TIC in stimulated cycles for couples with male subfertility, incorporating studies with varied stimulation regimens [12]. The authors found no significant improvement in pregnancy rates for stimulated cycles with IUI versus stimulated cycles with TIC for couples with male subfertility ($n=202$, OR 1.67, 95 % CI 0.83–3.37) [12].

13.4.2 Unexplained Infertility

Doubt about the effectiveness of IUI in unexplained infertility was raised many years ago and persists. Individual studies have been inconsistent on whether pregnancy rates are increased when IUI is added to COH [16–20]. Two early meta-analyses demonstrated a marginal benefit for IUI over TIC combined with COH with injectable gonadotropins for couples with unexplained infertility. Zeyneloglu et al. reported an OR for pregnancy of 1.84 (95 % CI = 1.30–2.62) among 980 cycles when IUI with FSH was compared to FSH alone [21]. Hughes reported an OR of 2.37 [95 % CI, 1.43, 3.90] for the same comparison, although they noted significant clinical heterogeneity among the 8 included trials [11]. Another study demonstrated a benefit, but the per-cycle pregnancy rate in the clomiphene citrate (CC) + IUI cohort was very low, at 3.16 %, a rate that is likely of limited acceptability to most couples [22].

Despite the aforementioned, limited number of studies documenting a small benefit for IUI for couples with unexplained infertility, these findings are not reproducible and multiple studies refute these findings. A recent meta-analysis consisting of seven trials comparing TIC with IUI in couples with unexplained infertility found no benefit for IUI [23]. Further, two recent randomized control trials also failed to demonstrate the benefit of IUI with ovarian hyperstimulation over TIC for couples with unexplained infertility. In the first study, 140 couples with unexplained infertility were randomly assigned to controlled

ovarian hyperstimulation (COH) with CC and either TIC or IUI [24]. There was no statistically significant difference in the pregnancy rate for the COH/TIC cohort (41 %) and COH/IUI (18 %) cohort over up to six cycles [24]. Another study of 157 couples with unexplained infertility randomized patients to compare outcomes of IUI, direct intraperitoneal insemination, and intercourse in cycles stimulated with CC or gonadotropins [16]. The results demonstrated that insemination cycles and intercourse cycles had a similar overall pregnancy rates of 12 % and 13 %, respectively, and the authors concluded that insemination had no beneficial effect on the pregnancy rates in stimulated cycles for treatment of unexplained infertility [16]. COH/IUI treatment has also been compared to expectant management in a study of 253 couples with unexplained infertility randomized to 6 months of IUI with controlled ovarian hyperstimulation versus 6 months of expectant management [25]. These investigators found that the conception rates of 33 % versus 32 % and ongoing pregnancy rates 23 % versus 27 % were not significantly different between the intervention group and the expectant management group, respectively (relative risk 0.85, 95 % CI 0.63–1.1), but the only triplet pregnancy was in the COH/IUI group [25]. Similarly, IUI does not increase clinical pregnancy or live birth rates for anovulatory women treated with CC with IUI versus TIC, with live birth rates per cycle 8.5 % with IUI and 7.9 % with TIC [26]. The failure to consistently demonstrate a benefit of IUI added to superovulation for unexplained infertility raises doubt that IUI offers any increase in the chances of successful pregnancy.

13.5 Cost-Effectiveness

Cost must also be considered when considering treatment strategies for infertility patients. Treatment costs associated with expectant management, oral CC, or unstimulated IUI were collected prospectively by Bhattacharya et al. [14, 27]. The cost analysis revealed the costs per live birth were £72 (95 % confidence interval £0–£206), £2611 (£1870–£4166), and £1487 (£1116–£2155) for expectant management, CC, and IUI, respectively. This led to an incremental increase in cost per additional live birth of £5604 with IUI, compared with expectant management, as depicted in Table 13.1 [14]. The authors concluded that empiric treatment with IUI for unexplained infertility was not associated with increased live birth rates and was unlikely to be a cost-effective treatment [27]. Custers et al. noted similar results in longitudinal assessment of the 253 couples with unexplained subfertility, initially randomized to expectant management or treatment with controlled ovarian stimulation IUI (COS-IUI) for 6 months [28]. After 3 years of follow-up, there was no difference between the groups in chances of pregnancy or time interval to pregnancy, but the COS-IUI group incurred an additional 2616 € in costs [28].

13.6 Adverse Events

In addition to an absence of consistent evidence supporting the efficacy and cost-effectiveness of IUI for various indications, one must also consider the risks and adverse effects associated with the IUI procedure. The adverse effects associated with the procedure include the discomfort of the procedure and the potential risk of infection. The risk of an infectious complication in women undergoing IUI has been reported to be 1.83 per 1,000 women undergoing the IUI procedure [29]. While IUI has not been shown to increase the rate of multifetal gestations, IUI is often performed in conjunction with superovulation or COH, which increases the risk of multifetal gestation far above that associated with natural conception cycles. An absence of registry information about non-ART treatments makes it difficult to analyze the contribution of ovarian stimulation plus IUI or ovulation induction plus IUI to multiple birth rates. A recent review reported the multiple pregnancy rates after non-ART ovarian hyperstimulation ranged from 10 % to 40 % per cycle and estimated the contribution of this treatment to the multiple birth epidemic to be approximately 30 % [30]. The authors noted the contribution of ovarian stimulation, with either ovulation induction

Table 13.1 Cost and effectiveness results

Treatment	Mean (SD) cost per treatment cycle[a] (£)	Mean (SD) number of treatment cycles per patient	Mean (SD) treatment cost per patient[b] (£)	Treatment cost difference versus EM (SE)	95 % CI for cost difference versus EM (*P* value) (£)	Live birth rate (per woman)	Odds ratio versus EM (95 % CI; *P* value)	Mean cost per live birth (95 % CI)[c] (£)
EM	0	–	11.88 (116.50)	–	–	0.17	–	71.64 (−27.02 to 191.51)
CC	83.12 (17.21)	4.10 (2.22)	349.96 (219.54)	338.08 (17.85)	303.39–370.02 (<0.0001)	0.13	0.78 (0.44–1.36; 0.3824)	2611.25 (1870.49 to 4166.46)
IUI	97.61 (31.12)	3.39 (2.01)	331.27 (222.15)	319.39 (18.06)	286.19–352.89 (<0.0001)	0.22	1.44 (0.87–2.40; 0.1584)	1486.87 (1116.48 to 2155.12)

[a]Weighted average, based on the total cost of treatment and the total number of treatment cycles provided in each center
[b]Incorporating the cost of adverse events
[c]Mean cost per live birth = Mean treatment cost per patient divided by live birth rate per woman (e.g., for EM: 11.88/0.17 = 71.64) (Reprinted with permission [27])

or superovulation, to triplet or higher-order multiple birth approaches 50 % [30].

In the USA between 1997 and 2000, ovarian stimulation and ovulation induction's contribution to the national multiple births increased from 18.9 % (20,955 infants) to 21.9 % (27,647 infants) [2]. The risk varies depending on the ovulation induction agent and dose. The estimated risk of multifetal gestation after treatment with CC and IUI is 8–10 % [31]. Rates of multiple gestations after gonadotropin stimulation with IUI are undoubtedly dependent upon individual clinical practices with regard to monitoring and cancellation of cycles; however, rates of twin and high-order multiples as high as 28.6 % and 8.2 %, respectively, have been reported [2]. Table 13.2 summarizes rates of multiple gestations reported with gonadotropin stimulation in a variety of studies [32].

The importance of these associated risks should not be underemphasized, as multifetal gestations are associated with significant risk to maternal, fetal, and neonatal health. Multifetal gestations carry increased risk of maternal complications including anemia, gestational diabetes, cesarean section, preeclampsia, postpartum hemorrhage, and mortality [30]. Adverse fetal and neonatal effects of multifetal gestations include infection, bleeding, prematurity, cerebral palsy, visual and hearing defects, and learning difficulties [30].

13.7 IUI Versus IVF

The effectiveness of IUI must be considered in comparison to in vitro fertilization (IVF), as multifetal gestations can be effectively prevented with IVF with elective single embryo transfer. Past studies comparing IUI and IVF become quickly dated as IUI success rates have remained stagnant, whereas IVF outcomes have continued to improve [4]. In a study published in 2000, Goverde et al. found similar per cycle and cumulative pregnancy rates with IVF, IUI, and COH/IUI and increased costs per live birth with IVF. However, the pregnancy rate per cycle in IVF was only 12.2 % [49]. In the USA, in 2010, the chances of live birth in an in vitro fertilization cycle were 41.7 % per initiated cycle and 47.8 % per embryo transfer for women under the age of 35 (SART 2010 National Data Summary). In the FASTT trial, women ages 21–39 with unexplained infertility were randomized to undergo three cycles of CC/IUI followed by three cycles of FSH/IUI, followed by IVF, or, to an accelerated track consisting of three cycles of CC/IUI followed by IVF. The investigators demonstrated not only increased pregnancy rates in the accelerated track but also a cost savings of $2624 per couple [50]. In data presented in abstract, the FORT-T Trial, by the same investigators demonstrated an increased live birth rate among women aged 38–43, undergoing immediate IVF compared with IUI preceded by either FSH or CC superovulation, with rates of 15.3 % and 5.1 %, respectively [51]. Thus, the use of COH-IUI appears to offer little benefit to patients, while increasing total costs and delaying the time to pregnancy.

Moreover, IVF with elective single embryo transfer (eSET) has been demonstrated to minimize the risks of multiple gestation associated with COH-IUI. In a recent randomized control trial evaluating outcomes after elective single embryo transfer (eSET) versus double embryo transfer (DET), no difference was demonstrated in the ongoing pregnancy rates for 61 % for eSET versus 76 % for DET (RR 0.80; p = NS), with twin rates of 47 % after DET and 0 % after eSET [52]. In another study, a single cycle of IVF with eSET was compared with three cycles of COH-IUI. Ongoing pregnancy rates were similar in the two arms, but there were no higher order multiples in the IVF group [53]. These studies clearly demonstrate the efficacy of IVF with eSET. There has been a gradual increase in the utilization of elective single embryo transfer in IVF over time worldwide [54]. This change in practice worldwide will likely continue to decrease multifetal gestations associated with IVF; however, similar options are not available to decrease multifetal gestations associated with COH-IUI. The disparity in multifetal gestations after COH-IUI versus IVF cycles will likely widen in the future as patient and provider acceptance of elective single embryo transfer continues to increase in IVF.

Table 13.2 Studies assessing multiple gestation risk associated with non-ART ovulation stimulation with gonadotropin medications or both gonadotropin and clomiphene or other anties trogenenic medications[a]

Author, year [reference number]	Study type	Time period	No. of women included	No. of total treatments	No. of pregnancies	Twin pregnancies		Triplet/+ pregnancies		Total multiple pregnancies	
						No.	%	No.	%	No.	%
Bedaiwy et al., 2007 [33]	Obs/P	2003–2006	389	630	94	16	17.0	3	3.2	19	20.2
Ragni et al., 2006 [34]	Obs/R	2001–2004	621	1,259	116	11	9.5	0	0	11	9.5
Matorras et al., 2006 [35]	Obs/R	2002–2003	NS	328	54	9	16.7	2	3.7	11	20.4
Gorry et al., 2006 [36]	Obs/R	1990–2002	199	916	91	3	3.3	0	0	3	3.3
Tur et al., 2005 [37]	Obs/P	2001–2002	NS	1,542	207	33	15.9	5	2.4	38	18.4
Mitwally et al., 2005 [38][b]	Obs/P	1999–2001	NS	671	95	NS	~12	0	0	NS	~12
Mitwally et al., 2005 [38][b]	Obs/P	1999–2001	NS	358	57	NS	~13	0	0	NS	~13
Dickey et al., 2005 [39]	Obs/R	1987–2002	2,272	4,067	587	108	18.4	38	6.5	146	24.9
Ibérico et al., 2001 [40]	Obs/R	2000–2002	470	1,010	93	NS	8.6	0	0	NS	8.6
Calaf Alsina et al., 2003 [41]	Obs/P	1988–1999	343	945	136	8	5.9	0	0	8	5.9
Tur et al., 2001 [42]	Obs/R	1988–1998	NS	NS	1,878	294	15.7	107	5.7	401	21.4
Schachter et al., 2001 [43]	Obs/R	1997–1999	220	480	129	11	8.5	3	2.3	14	10.9
Gleicher et al., 2000 [44]	Obs/R	1997–1998	1,494	3,347	441	88	20.0	39	8.8	127	28.8
Nuojua-Huttunen et al., 1999 [45]	Obs/R	1992–1996	NS	811	102	12	11.8	2	2.0	14	13.7
Ragni et al., 1999 [46]	NS	NS	273	449	51	12	23.5	1	2.0	13	25.5
De Geyter et al., 1998 [47]	Obs/R	1989–1996	410	796	163	15	9.2	5	3.1	20	12.3
Tadokoro et al., 1997 [48]	Obs/R	1991–1995	356	995	187	26	13.9	5	2.7	31	16.6
Posterior mean						12.32		1.99			
95% Credible interval						9.05	16.16	0.90	3.54		

ART assisted reproductive technology, *NS* not stated, *Obs/P* observational, prospective, *Obs/R* observational, retrospective, *RT* randomized trial, *triplet/+* triplet or higher order

[a]From each study, data for each non-ART ovulation treatment group that include ≥50 pregnancies were abstracted separately. Thus, some studies contributed more than one treatment group to summary calculations

[b]Exact numbers on twin pregnancies were not provided, but twinning rates were estimated from bar graphs. Triplet/+ pregnancies were stated as 0

(Reprinted with permission [32])

13.8 Cost-Effectiveness of IVF Versus IUI

Despite the greater cost per cycle of IVF compared with COH-IUI, cost-effectiveness data favors immediate IVF. Pashayan et al. used mathematical modeling to estimate the cost-effectiveness of first-line treatment with IVF (including cryopreservation cycles) versus initial treatment with either stimulated or unstimulated IUI followed by IVF for couples who did not become pregnant with IUI on 100 theoretical patients with male factor or unexplained infertility [55]. The authors concluded that for this hypothetical cohort of 100 couples, compared with an initial offer of IVF, six cycles of unstimulated IUI followed by IVF would cost an additional £174,200 and stimulated IUI followed by IVF would cost an additional £438,000 [55]. They also reported this cost in terms of the opportunity cost. The authors reported the opportunity cost for initiating treatment with unstimulated IUI followed by IVF was 54 IVF cycles and 14 live births and the opportunity cost of stimulated IUI followed by IVF was 136 IVF cycles and 35 live births for that health care system [55]. Although an individual may experience a cost saving if she were to become pregnant with stimulated or unstimulated IUI, these studies reveal an overall cost savings per live birth for a population of couples with male factor or unexplained infertility. Modeling from this study is depicted in Fig. 13.2.

IVF is widely accepted as preferred therapy for bilateral tubal obstruction, and severe oligozoospermia, where chances of conception with IUI are extremely low. In addition to a lack of evidence from randomized control trials supporting the utilization of IUI in male subfertility, there are inconsistent thresholds below which IUI would be an ineffective treatment option [4, 56, 57]. One retrospective study of more than 1,800 patients concluded that pregnancy rates were at least 8.2 % when initial sperm values

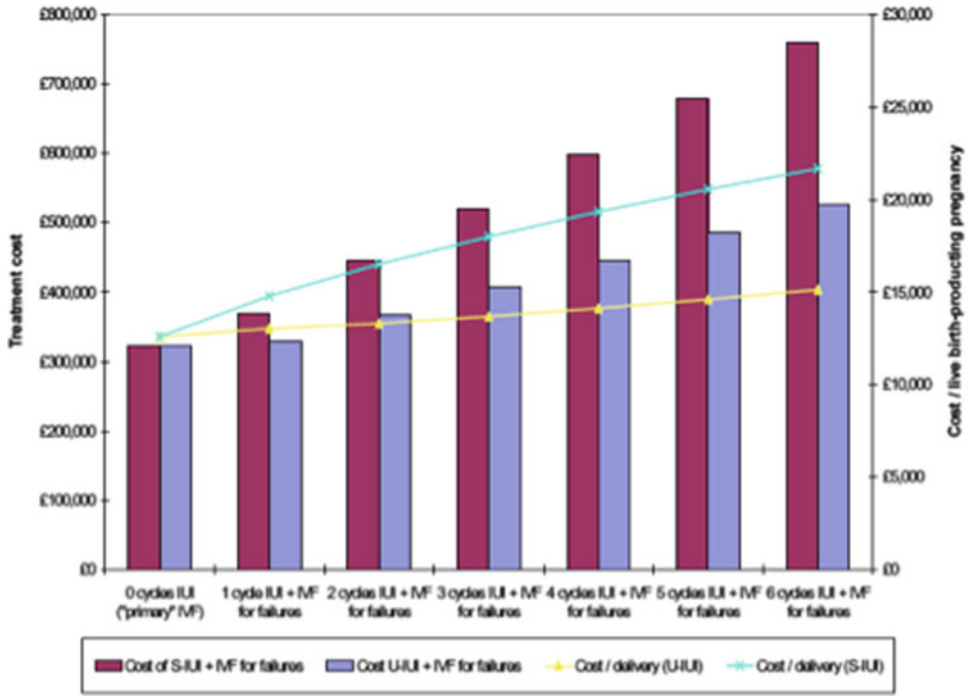

Fig. 13.2 Cost and cost-effectiveness (per live birth-producing pregnancy) of different uptake of IUI and S-IUI among a hypothetical cohort of 100 couples eligible for both IUI and IVF. Assume constant LBR of 7 % and 3.5 % for S-IUI and IUI (Reprinted with permission from Pashayan et al. [39])

demonstrated greater than or equal to a concentration of two million per mL, a total count of ten million, progressive motility of 30 %, and a total motile sperm count of five million [58]. These authors reported pregnancy rates less than 3.6 % when initial sperm values were below these thresholds, but above the lowest initial sperm values associated with a pregnancy: a concentration of two million per mL, a total count of five million, motility of 17 %, and a total motile sperm count of 1.6 million [58].

A second retrospective study of over 2,400 IUI cycles reported pregnancy rates of 5.3 % if the semen analysis demonstrated less than five million motile sperm versus 12.8 % with samples greater than five million motile sperm ($p < 0.02$) [57]. A third retrospective study looked at the relative effectiveness and cost-effectiveness based on sperm counts in 3,479 IUI cycles and 551 IVF cycles [56]. These investigators concluded that when the average total motile sperm count was under ten million, IVF with ICSI was more cost-effective than IUI, and proposed that an average total motile sperm count of less than ten million be used as a threshold for recommending IVF with ICSI over IUI [56]. These discrepant thresholds further complicate the decision making for patients and providers considering treatment options in cases of male factor subfertility. Regardless of the ideal threshold for recommending IVF over IUI in cases of male factor subfertility, the fact remains there is an absence of clear data from well-designed randomized studies supporting the utilization of IUI in cases of male factor infertility [12].

13.9 Conclusion

Current evidence fails to support the continued utilization of IUI for male factor or unexplained infertility. The IUI procedure is often performed in conjunction with ovulation induction or controlled ovarian stimulation, which is associated with an inherent, excessive, and unavoidable risk of producing a multifetal gestation. Further, despite the chance that an individual may experience a cost saving if a pregnancy were achieved after COH/IUI, studies considering a population of infertile patients do not support the utilization of IUI as a cost-effective treatment. Thus, based on a lack of data demonstrating efficacy, cost considerations, and the adverse effects associated with the procedure as it is typically performed, IUI should no longer be offered as part of routine treatment in modern day infertility practices.

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