

## APPENDIX C: Details of included studies

Paper	Score	Objectives	Search strategy	Selection criteria	Analysis	Results and Conclusions
Agrawal R, Holmes J, Jacobs HS (2000) Follicle-stimulating hormone or human menopausal gonadotropin for ovarian stimulation in in vitro fertilization cycles: a meta-analysis <i>Fertility and Sterility</i> <b>73</b> (2) 338-343	15	To reanalyse the results of using FSH alone and hMG during IVF treatment, taking into account the different protocols of administration of superactive GnRH agonist analogs.	MEDLINE search from January 1985 to March 1999. Manual search of review articles and abstracts of major scientific meetings and conference proceedings from 1985 to 1999, and of studies not in English.	RCTs comparing the effect of FSH or hMG in infertile women undergoing IVF treatment. Acceptable studies were grouped into 3 categories according to the type of GnRH protocol used: short, long or none. Exclusions: retrospective analyses, crossover trials, trials using clomiphene citrate or a combination of FSH and hMG. Main Outcome Measure: Clinical pregnancy rate per cycle of IVF.	5 eligible studies with no GnRH agonist, 1 with short protocol, and 11 with long protocol. Meta-analysis: the common Peto odds ratio was calculated with use of a fixed effect model. The overall log odds ratio was estimated after demonstrating the consistency or homogeneity of the study results.	<b>Results:</b> The results suggested that in the "long and short GnRH agonists protocol" of IVF, FSH, and hMG were equally effective in achieving ovarian stimulation, and there were no differences in the clinical pregnancy rates per cycle of IVF. However, in protocols where no pituitary desensitisation was used, FSH alone was more efficacious. <b>Conclusions:</b> The optimum choice of gonadotropin preparation for ovarian stimulation during IVF treatment is influenced by the regimen of pituitary desensitisation used. The optimum gonadotropin to be used when GnRH antagonists are used has yet to be determined.
Blake D, Proctor M, Johnson N and Olive D (2002) Cleavage stage versus blastocyst stage embryo transfer in assisted conception. In <i>The Cochrane Library</i> Issue 4. Update Software, Oxford	22	Primary: To determine if blastocyst stage (day 5/6) embryo transfers (ET's) result in higher success rates than cleavage stage (day 2/3) embryo transfers. Secondary: to assess the overall embryo utilisation rate of both techniques.	Search of Cochrane Menstrual Disorders and Subfertility group register of controlled trials, Cochrane Controlled Trials Register, MEDLINE, EMBASE, Bio extracts. Citation lists of review articles and included trials.	Trials were included if they were randomised and compared the effectiveness of early cleavage versus blastocyst stage transfers. Quality assessment and data abstraction were performed independently by two reviewers. Primary outcomes were rates of live birth, clinical pregnancy and implantation per woman. Secondary outcomes were rates of miscarriage, monozygotic twinning, embryo freezing, embryo utilisation, cancellation, multiple pregnancy, high order pregnancy and per cycle data	Of the 29 trials identified, 10 were included. Meta-analysis was performed using odds ratios for dichotomous outcomes and weighted mean differences for continuous outcomes. Heterogeneity was examined by formal chi-squared test, and by inspecting the scatter of data points and overlap in CIs. Quasi-randomised trials were analysed as a separate subgroup.	<b>Result(s):</b> There was no significant difference in live birth rate (1 trial, Peto OR 1.59, 95% CI 0.80, 3.15), and no evidence of a difference in pregnancy rate (4 RCTs, Peto OR 0.86, 95% CI 0.57, 1.29), miscarriage rate, multiple pregnancy rate, or implantation rate (17% v 19%, no CIs). Implantation rate in sequential media trials was higher in Day 5/6 group (22% v 32%). Embryo transfer rates were significantly higher in the Day 5/6 group (5 RCTs, Peto OR 0.57, 95% CI 0.40, 0.83). <b>Conclusions:</b> Little difference in the major outcome parameters has been demonstrated. The increase in cancellation and possible decrease in cryopreservation rates suggest that the routine practice of blastocyst culture should be offered to patients with caution. The subgroup of sequential media trials showed a substantial improvement in implantation rates and similar pregnancy rates, despite the transfer of fewer embryos. Whether this trend will culminate in higher live birth rates per woman has yet to be evaluated.
Evers JLH, Collins JA, Vandekerckhove P (2000) Surgery or embolisation for varicocele in subfertile men <i>Cochrane Library</i> Issue 4 (2002)	24	To evaluate the effect of varicocele treatment on pregnancy rate in subfertile couples.	Cochrane Menstrual Disorders and Subfertility Group's specialised register of controlled trials; MEDLINE search (1966-2000); hand-search of 22 core journals up to 2000; references from articles.	Potentially relevant trials were screened independently by two authors. A trial was eligible for inclusion if it dealt with the treatment of varicocele in subfertile couples where the male partner had a left-sided varicocele and normal or abnormal semen analysis, and contained a control group which the authors claimed was created by a randomisation procedure. Pregnancy rate was the only outcome measure.	5 eligible studies met the inclusion criteria. The results of a WHO megatrial were not yet available. Meta-analysis using Peto-modified Mantel-Haenzel method, with a random effects model as there was clinical and statistical heterogeneity. Given the small numbers of patients in these studies a subgroup analysis was considered inappropriate.	<b>Results:</b> Over all, these were not all high quality studies. One trial (Madgar 1995) reported a statistically significant improvement in pregnancy rate following high ligation of the left spermatic vein. None of the other four studies showed individually a significant effect on pregnancy rates of varicocele treatment over no treatment, or over counselling only. The combined RR (Relative Risk, random effects method) of the five studies is 1.06 (95%CI 0.57-1.94), the Peto OR (Odds Ratio) is 1.15 (95%CI 0.73-1.83). <b>Conclusions:</b> Insufficient evidence exists that treatment of varicocele in men from couples with otherwise unexplained subfertility does improve the couple's spontaneous pregnancy chances. However as the confidence interval is wide and the studies are heterogeneous, a large, properly conducted RCT is needed.

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Honoré GM, Holden AE and Schenken RS (1999) Pathophysiology and management of proximal tubal blockage <i>Fertility and Sterility</i> <b>71</b> 785-95	10	To review the physiology, pathology and treatment of proximal tubal disease.	MEDLINE search (dates not specified) and cross-referencing to Science Citation Index. English language only. Abstracts from scientific meetings were not considered.	Inclusions: macrosurgery, microsurgery, radiographic methods or hysteroscopic treatments. Bilateral gross or microsurgical anastomoses and bilateral transcervical microsurgery. Exclusions: mid or distal tubal disease, combined procedures, sterilisation reversals, series where cause of blockage could not be determined, case reports or small case series. Outcome measures: total pregnancy rate, ongoing pregnancy rate.	No RCTs were identified, so cohort and observational studies (case series) were used: 18 on surgery, 17 on radiographic transcervical methods, 6 on hysteroscopy. Raw data were assessed for homogeneity, standardised and pooled. Chi-squared tests and relative risks compared total and ongoing pregnancies after microsurgery, macrosurgery and radiographic and hysteroscopic cannulation.	<b>Results:</b> Overall, microsurgical anastomosis results in higher total (59%) and ongoing pregnancy rates (47%) than macrosurgery (36% and 22%) or radiographic tubal cannulation (21% and 26%), but not than hysteroscopic surgery (49% and 49%). However pregnancy rates in selected series of transcervical tubal cannulation are similar to those for microsurgery. <b>Conclusions:</b> Ongoing intrauterine pregnancy rates near 50% can be achieved in patients with proximal blockage of the fallopian tube. Selective salpingography and transcervical cannulation under fluoroscopic guidance are effective at establishing patency in appropriately selected patients and are less invasive and costly than the surgical alternatives.
Tournaye H, Verheyen G, Albano C, Camus M, Van Landuyt L, Devroey P and Van Steirteghem A (2002) Intracytoplasmic sperm injection versus in vitro fertilization: a randomized controlled trial and a meta-analysis of the literature <i>Fertility and Sterility</i> <b>78</b> 1030-1037	16	To compare ICSI with IVF using two insemination concentrations in moderate male infertility and to compare these data with other RCTs. (the summary in this table only describes the meta-analysis)	MEDLINE and EMBASE search (dates not specified), and manual search of references from the studies obtained by the electronic search.	Randomised controlled studies In all studies identified, sibling oocytes were randomised between IVF, either standard or high insemination concentration (HIC), and ICSI, but mixed embryo transfers were performed. Thus the only outcome measures available were fertilisation rate and fertilisation failure.	9 studies identified, including the RCT reported here; 2 of these had 2 subsets of patients. 2 groups of patients had isolated teratozoospermia; 9 groups, including 3 where HIC IVF was used, had borderline semen characteristics. Meta-Analysis software was used to perform meta-analysis with a random effects model.	<b>Results:</b> The risk ratio for an oocyte to become fertilised was 1.9 (95% CI 1.4, 2.5) in favour of ICSI, and 3.1 ICSI cycles may be needed to avoid one complete fertilisation failure after conventional IVF (95% CI 1.7, 12.4). In subgroup analyses, the RR of fertilisation was 1.1 (95% CI 0.8, 1.7) in patients with teratospermia, 2.2 (95% CI 1.6, 3.0) in patients with borderline semen characteristics, and 1.1 (95% CI 0.7, 1.7) in the studies where HIC IVF was used. <b>Conclusions:</b> The data from the RCT and meta-analysis show ICSI is a more efficient technique in terms of fertilisation, but not in comparison with HIC IVF.
Zeyneloglu HB, Arici A, Olive DL, Duleba AJ (1998) Comparison of intrauterine insemination with timed intercourse in superovulated cycles with gonadotropins: a meta-analysis <i>Fertility and Sterility</i> <b>69</b> 486-491	16	To compare timed intercourse and IUI with the husband's sperm in patients with unexplained infertility who are undergoing superovulation with gonadotropins.	MEDLINE search from 1966 to 1997. Manual search of bibliographies of relevant publications and review articles.	Prospective randomised studies. Trials using hMG or FSH treatments were included, but those with CC alone were excluded. Couples with: $\geq 2$ year history of infertility, spontaneous ovulation, male partner with $\geq 2$ normal semen analyses, and tubal patency shown by diagnostic laparoscopy Primary outcome was clinical pregnancy rate (PR)	7 eligible studies. Quality of individual studies was assessed. Meta-analysis using Peto method and a fixed-effects model to obtain the common odds ratio and 95% confidence intervals. Homogeneity was tested with the Breslow-Day test.	<b>Results:</b> There were 49 pregnancies in 431 cycles of timed intercourse (11.4%), whereas there were 110 pregnancies in 549 cycles of IUI (20.0%). The PRs for IUI were significantly increased compared with those for timed intercourse in superovulation cycles (common OR 1.84, 95% CI 1.30-2.62). <b>Conclusions:</b> A patient's chance of becoming pregnant are greater with IUI with her husband's sperm than with timed intercourse in cycles superovulated with gonadotropins. Thus IUI may help some couples avoid the cost and inconvenience of more invasive techniques, such as IVF or GIFT. The analysed studies had only moderate validity scores, so a large RCT should be considered.