Fertility RESEARCH REVIEW™

Making Education Easy

Issue 39 – 2024

In this issue:

Abbreviations used in this issue

ART = assisted reproductive technology
BMI = body mass index
ET = embryo transfer
GLP-1 = glucagon-like peptide 1
hCG = human chorionic gonadotropin
ICSI = intracytoplasmic sperm injection
IVF = in vitro fertilisation
PCOS = polycystic ovary syndrome
PRP = platelet-rich plasma
RCT = randomised controlled trial

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Welcome to the latest issue of Fertility Research Review.

In this issue, the BAMBINI trial evaluates the impact of bariatric surgery on ovulation in obese women with anovulatory PCOS, a large study provides reassuring evidence that storage time of vitrified embryos has no effect on ART outcomes, Spanish investigators report that fresh sperm may be better than cryopreserved sperm for ICSI cycles, and investigators in Israel find that testicular fine-needle aspiration is a worthwhile first step in surgical sperm retrieval from men with non-obstructive azoospermia.

We hope you find these and the other selected studies interesting and look forward to receiving any feedback you may have.

Kind regards,

Dr Leigh Searle
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Bariatric surgery for spontaneous ovulation in women living with polycystic ovary syndrome

Authors: Samarasinghe SNS et al.

Summary: The multicentre BAMBINI trial evaluated the impact of bariatric surgery on ovulation rates in women with PCOS, obesity, and oligomenorrhoea or amenorrhoea. Eighty women (median age 31 years) with PCOS and BMI ≥35 kg/m^2 were randomised 1:1 to either vertical sleeve gastrectomy (surgical group) or weight loss medication + lifestyle interventions (medical group). During 12 months of follow up, the median number of ovulations was six in the surgical group and two in the medical group. Women in the surgical group were significantly more likely to have spontaneous ovulation than those in the medical group (incidence rate ratio 2.5, 95% CI 1.5–4.2; p<0.0007), but had a higher incidence of adverse events (66.7% vs 30.0%).

Comment: This is an important RCT comparing treatments for obesity in those with anovulatory PCOS. It compared laparoscopic sleeve gastrectomy with lifestyle interventions and pharmacotherapy with metformin ± orlistat (this was before GLP-1 agonists were available; see next study). A significant average weight loss (36kg) was recorded in the surgical group compared to nil average weight loss in the medical group. Significantly more spontaneous ovulations occurred in the surgical group, however interestingly there were two pregnancies in the medical group and one in the surgical group. The surgical group had more adverse events, including cholecystitis and wound infections. Both groups had incidences of nutritional deficiencies. As well as improving ovulation this reduction in weight will also reduce obstetric risk during pregnancies.

Reference: Lancet 2024;403(10443):2489–503

Abstract

INDEPENDENT COMMENTARY BY

Dr Leigh Searle

Leigh is an obstetrician and gynaecologist who has completed subspecialty training in reproductive endocrinology and infertility. Leigh trained in NZ and completed a fellowship at the Royal Women's Hospital in Melbourne where there was a strong focus on fertility preservation. Leigh was the first person in NZ to perform an ovarian tissue graft from previously cryopreserved ovarian tissue. Leigh is director of training for Fertility Associates NZ and sees both fertility and gynaecology patients at Fertility Associates Wellington and regularly travels to Palmerston North to consult. **For full bio CLICK HERE.**

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Treating obesity and fertility in the era of glucagon-like peptide 1 receptor agonists

Authors: Goldberg AS & Boots CE

Summary: This narrative review discussed the management of women with obesity and infertility with regard to the recent availability of GLP-1 receptor agonists. Women with an increased BMI have less successful reproductive outcomes, and weight loss may be appropriate for some of them as part of their infertility treatment plan. Recently, medications such as GLP-1 receptor agonists that treat neuroendocrine hormone imbalances have been shown to produce meaningful weight loss comparable to surgical interventions. It is important to increase our understanding of the mode of action, adverse effects, and implications for pregnancy of these agents, and whether they can be used to improve fertility outcomes and/or access to fertility care.

Comment: It is well established that those with obesity have a higher chance of fertility delay and of having comorbidities that increase obstetric risk (e.g. hypertension, diabetes etc). Growing numbers of people are taking GLP-1 receptor agonists for treatment of diabetes and/or obesity. Current recommendations encourage discontinuation before conception; however, the preconception use of these agents may have important benefits and possible risks. It has been suggested that GLP-1 receptors exist in the reproductive system but as yet we do not know the effects on fertility. The benefits of using these medications preconception include improved insulin sensitivity and other metabolic parameters associated with higher BMIs, such as blood pressure and inflammation. In a single prospective study of 27 participants, an improved embryo implantation rate after pretreatment with a short-acting GLP-1 receptor agonist (liraglutide) before IVF was reported. The investigators hypothesised that the anti-inflammatory properties of this medication may positively affect the endometrium and enhance receptivity and implantation. However, there is concern regarding nutritional deficits and the altered metabolism noted during acute weight loss that may affect pregnancy and neonatal outcomes. Acute weight loss may be associated with improved ovulation and spontaneous conceptions. This medication will be one to watch as we get more data.

Reference: Fertil Steril. 2024;122(2):211–8
Abstract

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Fertility Research Review **CLICK HERE**

Effectiveness of preconception weight loss interventions on fertility in women

Authors: Caldwell AE et al.

Summary: This systematic review and meta-analysis examined the effectiveness of preconception weight loss interventions in women with overweight or obesity. A search of various databases identified a number of eligible RCTs that reported fertility outcomes after weight loss interventions (lifestyle and/or medication); 16 studies reported pregnancies (n=3588), 13 reported live birth rates (n=3329), and 11 reported miscarriage events (n=3248). Meta-analysis of the data showed that women randomised to weight loss interventions were significantly more likely than controls to become pregnant (risk ratio [RR] 1.24, 95% CI 1.07–1.44) but not to have a live birth (RR 1.19, 95% CI 0.97–1.45) or miscarriage (RR 1.17, 95% CI 0.79–1.74). Subgroup analyses revealed that women who received weight loss interventions for up to 12 weeks and those with initial BMI ≥35 kg/m^2 were more likely to become pregnant than those in control groups.

Comment: This study included RCTs looking at weight loss interventions in women planning pregnancy. The lifestyle intervention trials used dietary approaches including caloric restriction or meal replacement with some including physical activity. Two studies included lifestyle and pharmaceutical interventions such as orlistat or liraglutide. Control groups varied but many had a meeting with a dietician or daily steps goals as part of "usual care". Live births were higher but not statistically significantly so in the intervention group compared to controls. Subgroup analysis of those with BMI >35 showed higher pregnancy rates in the intervention group compared with controls. There was no data on weight loss threshold for improving fertility outcomes. This study suggests that a personalised approach to weight loss interventions is most beneficial and should be supervised by clinicians with expertise in obesity treatment.

Reference: Fertil Steril. 2024;122(2):326–40
Abstract

Embryo long-term storage does not affect assisted reproductive technologies outcome: Analysis of 58,001 vitrified blastocysts over 11 years

Authors: Cobo A et al.

Summary: This retrospective study evaluated the effects of embryo storage time on ART outcomes. 58,001 vitrified/warmed day-5 blastocysts were compared for two ART modes (freeze-all cycles and nonelective frozen ETs [FETs]) over an 11-year period. Storage durations ranged from ≤0.67 to ≥4.34 months and from ≤1.8 to ≥34.81 months in freeze-all and nonelective FET groups, respectively. Multivariable analysis showed no association between storage time and live birth rate in either group.

Comment: This large study has reassuringly showed that there is no effect of storage time of vitrified embryos on clinical outcomes such as live birth. This is really important data as many more people rely on FETs to complete their families, often many years after egg collection. In NZ the Human Assisted Reproductive Technology (HART) Act allows storage of embryos for up to 10 years, requiring Ethics Committee on Assisted Reproductive Technology (ECART) approval to prolong this time if this is needed.

Reference: Am J Obstet Gynecol. 2024;231(2):238.e1–11
Abstract

Clinical effectiveness and safety of time-lapse imaging systems for embryo incubation and selection in in-vitro fertilisation treatment (TILT)

Authors: Bhide P et al.

Summary: This study evaluated the effectiveness of time-lapse imaging systems for embryo incubation and selection in IVF treatment. At seven IVF centres in the UK and Hong Kong, 1575 women undergoing IVF or ICSI were randomised 1:1:1 to the time-lapse imaging system for undisturbed culture and embryo selection (time-lapse imaging group), the time-lapse imaging system for undisturbed culture alone (undisturbed culture group), and standard care without time-lapse imaging (control group). Live birth rates did not differ significantly between groups: 33.7% in the time-lapse imaging group, 36.6% in the undisturbed culture group, and 33.0% in the standard care group.

Comment: This is a well-designed RCT comparing time-lapse with morphokinetics to time-lapse incubator alone to standard non time-lapse incubators, to answer the question if there is a shorter time to pregnancy between these three incubation methods for embryos. This allows investigation if there is a benefit of undisturbed culture with or without morphokinetic data compared to standard incubation. There was no statistically significant difference between these groups in live births. It has been proposed that morphokinetics may be a noninvasive way to assess for embryonic aneuploidy, however even when analysis was performed in women aged >35 with expected higher rates of aneuploidy there was no improvement in live birth rates using time-lapse morphokinetics. The benefit for the embryology lab workflow has not been assessed and this is where time-lapse may find its benefit.

Reference: Lancet 2024;404(10449):256–65
Abstract

Association between the length of in vitro embryo culture, mode of ART, and the initial endogenous hCG rise in ongoing singleton pregnancies

Authors: Brockmeier C et al.

Summary: This Danish cohort study investigated the association between the length of in vitro embryo culture, mode of ART, and the initial endogenous hCG rise in cycles resulting in a singleton ongoing pregnancy. Prospectively collected data for 4938 women undergoing IUI or ART treatments (2395 frozen ET (FET) cycles, 2521 fresh ET cycles, and 608 IUI cycles) that resulted in a singleton pregnancy were analysed. Serum hCG levels were significantly lower in pregnancies achieved after fresh ET (cleavage-stage or blastocyst transfer) than after IUI. In FET cycles, serum hCG was significantly higher after blastocyst transfers than cleavage-stage transfers. Regarding the ART mode, serum hCG was significantly higher after blastocyst-stage FET than fresh ET, while there was no difference after cleavage-stage FET versus fresh ET.

Comment: It is well known that there is large variation in what a "normal" serum hCG level is when monitoring in the first trimester and this monitoring can be a great source of anxiety for patients undergoing fertility treatment. Cleavage stage embryos had lower serum hCG compared to after IUI and hCG was higher for fresh cleavage stage transfer compared to fresh blastocyst. This was the opposite for frozen, with blastocyst transfers higher than cleavage stage. It is proposed that the ovarian stimulated uterine environment in fresh ET may cause differences in hCG levels compared to frozen cycles. These data suggest that the difference in serum hCG levels may be more associated with early embryo development and embryo culture rather than uterine environment as no difference was found between differing endometrial preparation types in frozen cycles.

Reference: Hum Reprod. 2024;39(7):1442–8
Abstract

Effect of intraovarian platelet-rich plasma injection on IVF outcomes in women with poor ovarian response

Authors: Herlihy NS et al.

Summary: The PROVA trial investigated the effects of intraovarian PRP injections on the number of mature oocytes obtained after controlled ovarian stimulation in women with poor ovarian response undergoing IVF. Eighty-three women aged <38 years with poor ovarian response (≥2 prior cycles with <3 oocytes retrieved) were randomised to receive autologous intraovarian PRP injection (n=41) or no intervention (n=42). The primary end-point (number of metaphase II oocytes retrieved per cycle after controlled ovarian stimulation) did not differ significantly between groups.

Comment: Decreased ovarian reserve affects a significant number of people undergoing fertility treatment, resulting in a higher chance of cycle cancellation, lower numbers of blastocysts and lower pregnancy rates. Retrospective studies have suggested that PRP treatment of the ovary may improve ovarian reserve parameters and response to treatment. This study looked at women aged 18–37 with reduced ovarian reserve (POSEIDON criteria) and randomised between PRP and no intervention with blinding of both those performing egg collection and embryologists. There were no statistically significant differences in oocyte numbers or ongoing pregnancy rates between groups and so this study does not support use of PRP in these patients.

Reference: Hum Reprod. 2024;39(7):1495–1503
Abstract

Double versus single stimulation in young low prognosis patients followed by a fresh embryo transfer

Authors: Racca A et al.

Summary: The DUOSTIM-fresh trial investigated reproductive outcomes after double versus single ovarian stimulation followed by fresh ET in low prognosis patients. 120 women aged <40 years with low pregnancy prognosis (anti-Müllerian hormone <1.2 ng/ml) were randomised to double ovarian stimulation (intervention group) or single ovarian stimulation (control group). The double stimulation group received ovarian stimulation in both the luteal and follicular phases of the same cycle, whereas controls received ovarian stimulation in the follicular phase only. The double stimulation group had a significantly higher number of good quality blastocysts compared with controls, although the mean percentage of cycles with embryo transfer was comparable (62.3% and 51.9%, respectively). No significant between-group differences were found for clinical outcomes after fresh ET; ongoing pregnancy rates were 24.5% and 22.2% in the respective groups.

Comment: We know that there are multiple waves of follicular development in the ovary and this is what underpins the option of multiple ovarian stimulations in one menstrual cycle. This is often used in those undergoing egg freezing prior to oncology treatment but is also a way of trying to obtain embryos in a shorter amount of time in those with lower ovarian reserve. This study tried alternative dual stim where the first stim was in the luteal phase and second in the follicular phase, allowing for fresh transfer following the second ovarian stimulation in this group compared to a control group that had standard ovarian stimulation commenced in follicular phase with fresh transfer if able. The dual stim group had a higher embryo transfer rate and a nonsignificantly higher pregnancy rate. A larger study would be interesting to investigate this further but this study suggests a promising approach for those with reduced ovarian reserve with live birth as an outcome. The downside of starting ovarian stimulation in the luteal phase means that there would be a small chance of a pregnancy yet undiagnosed during a luteal stimulation which is not ideal.

Reference: Hum Reprod. 2024;39(7):1548–57
Abstract

Assessment of reproductive outcomes of fresh versus cryopreserved ejaculated sperm samples – a retrospective analysis of 44 423 oocyte donation ICSI cycles

Authors: Juliá MG et al.

Summary: This multicentre Spanish cohort study compared reproductive outcomes after use of fresh versus cryopreserved ejaculated sperm samples for oocyte donation ICSI cycles. 37,041 couples and 44,423 ICSI procedures from Jan 2008 to Jun 2022 were analysed. ICSI procedures that used frozen sperm had slightly lower biochemical (2.56% vs 3.55%), clinical (3.54% vs 3.68%) and ongoing (3.15% vs 3.63%) pregnancy rates than those that used fresh sperm. Live birth rate was 3.95% lower per embryo transfer in the frozen sperm group than the fresh sperm group.

Comment: This study assessed the difference between fresh and frozen ejaculated sperm when using ICSI to fertilise donor oocytes (presumed fertile donors aged 18–35). This study suggests a small but significant reduction in live birth for first embryo transfer and also with cumulative live birth per embryo transfer when cryopreserved sperm compared to fresh sperm is used for ICSI with donor eggs. This study used donor eggs to try to reduce the effect of egg quality on results (egg donors presumed to have superior egg quality to those with subfertility). This was a retrospective study so further prospective studies would be helpful to confirm these results. Note there were some significant between-group differences in baseline characteristics (the frozen sperm group had older male age, longer duration of infertility, lower number of oocytes donated, and higher rates of male factor infertility) that may have affected birth rates as these are all possible confounding factors. Cryopreserved sperm can be a helpful technology within a fertility clinic for scheduling and is needed for quarantine requirements for donor sperm.

Reference: Hum Reprod. 2024;39(7):1381–9
Abstract

Testicular fine-needle aspiration in infertile men with absolute non-obstructive azoospermia

Authors: Sakas J et al.

Summary: This Israeli cohort study evaluated sperm retrieval rates after testicular fine-needle aspiration in infertile men with absolute non-obstructive azoospermia. Eighty-nine infertile men aged 26–47 years diagnosed with non-obstructive azoospermia were included and underwent testicular fine needle aspiration. Sperm cells were successfully retrieved from 40 (45%) men, with no significant postoperative complications. Of the successful procedures, 25% resulted in retrieval of up to 10 sperm cells, 22.7% retrieved dozens of sperm cells, and 52.3% retrieved 100s to 1000s of sperm cells. Men whose testicular fine needle aspiration resulted in only a few sperm cells had a much lower fertilisation rate than those with higher levels of sperm retrieval.

Comment: People with non-obstructive azoospermia are commonly seen in fertility practice. It is common practice to proceed with testicular fine needle aspiration prior to proceeding to open techniques if no sperm is found with this procedure. 45% of those in this series had sperm retrieved with this technique with no significant complications, confirming that this is a worthwhile first step in surgical sperm retrieval which will avoid open procedures in a significant number of men with non-obstructive azoospermia.

Reference: Aust N Z J Obstet Gynaecol. 2024;64(3):258–63
Abstract