

Fertility Research Review™

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Issue 21 - 2019

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Abbreviations used in this issue

ART = assisted reproductive technology
FSH = follicle stimulating hormone
ICSI = intracytoplasmic sperm injection
IUI = intrauterine insemination
IVF = in vitro fertilisation
HR = hazard ratio
OHSS = ovarian hyperstimulation syndrome
OR = odds ratio
RR = relative risk



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Welcome to the 21st issue of Fertility Research Review.

In this issue we review several studies in large population cohorts. One study in >47,000 children found the likelihood of cancer was not increased in children born after ART compared with those conceived spontaneously. Another study in >80,000 women found that nurses who worked rotating night shifts had a greater likelihood of earlier menopause than women who did not work rotating night shifts. We hope you enjoy these and our other selections for this issue and welcome your comments and feedback.

If you have colleagues or friends within New Zealand who would like to receive our publication, send us their contact email and we will send them a copy of the next issue.

Kind regards,

Dr Mary Birdsall

marybirdsall@researchreview.co.nz

Frozen versus fresh single blastocyst transfer in ovulatory women

Authors: Wei D, et al.

Summary: Frozen single blastocyst transfer resulted in a higher singleton live birth rate than fresh single blastocyst transfer in a multicentre randomised trial in 1650 women with regular menstrual cycles undergoing their first cycle of IVF. The singleton live birth rate was 50% after frozen embryo transfer vs 40% after fresh embryo transfer (RR 1.26; 95% CI 1.14–1.41; $p < 0.0001$). There were no significant differences between frozen or fresh embryo transfer in the risks of moderate or severe OHSS (0.5% vs 1.1%) and pregnancy loss (23.0% vs 25.8%), however, an increased risk of pre-eclampsia was observed after frozen embryo transfer (3.1% vs 1.0%; RR 3.3; 95% CI 1.06–9.30; $p = 0.029$). Other obstetric complications and neonatal morbidity were similar for frozen vs fresh embryo transfer.

Comment: Another impressive study from China looking at the very important question of fresh vs frozen embryos. This study found a significantly higher chance of having a baby with a frozen embryo transfer compared to a fresh transfer. At Fertility Associates we have seen the same take-home baby rate from fresh and frozen transfers, but this study provides more meaningful data as the best embryo was randomly assigned to either being transferred fresh or frozen. The increased risk of pre-eclampsia with the use of frozen embryos merits further work and may be associated with pregnancies without a corpus luteum.

Reference: *Lancet*. 2019;393(10178):1310-1318.

[Abstract](#)

Physiological, hyaluronan-selected intracytoplasmic sperm injection for infertility treatment (HABSelect)

Authors: Miller D, et al.

Summary: Physiological ICSI using hyaluronan-based sperm selection did not significantly improve live birth rates compared with standard ICSI in a randomised trial of 2772 couples undergoing an ICSI procedure with fresh embryo transfer. The full-term live birth rate (gestational age ≥ 37 weeks) was 27.4% with physiological ICSI and 25.2% with standard ICSI (OR 1.12; 95% CI 0.95–1.34; $p = 0.18$).

Comment: It is important that treatment options in the IVF world are appropriately researched to ensure the interventions are both safe and effective. Physiological ICSI was thought to be able to select sperm that were mature and had less DNA fragmentation compared to conventional ICSI and therefore may result in more healthy pregnancies. Physiological ICSI has been offered and charged for by many IVF units for more than 5 years and now the largest trial has shown no benefit. Physiological ICSI should no longer be offered as a sperm selection tool.

Reference: *Lancet*. 2019;393(10170):416-422.

[Abstract](#)

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Levothyroxine in women with thyroid peroxidase antibodies before conception

Authors: Dhillon-Smith RK, et al.

Summary: Use of levothyroxine did not increase the live birth rate in a double-blind, placebo-controlled trial in 952 euthyroid women with thyroid peroxidase antibodies. Women were randomised to receive levothyroxine 50 µg or placebo once daily before conception and through to the end of the pregnancy. The live birth rate (gestational age ≥ 34 weeks) was 37.4% in women who received levothyroxine and 37.9% in women who received placebo (RR 0.97; 95% CI 0.83–1.14; $p=0.74$). Pregnancy loss, preterm birth and other neonatal pregnancy or neonatal outcomes were not significantly different for women who received levothyroxine or placebo.

Comment: Thyroid function testing is a routine investigation for women with infertility and recurrent pregnancy loss. Women who are found to be thyroid antibody positive are keen to have an intervention that improves their prognosis. This large trial is useful as it demonstrates that women who have normal thyroid function and who are thyroid antibody positive do not benefit by the addition of thyroxine.

Reference: *N Engl J Med.* 2019;**380(14):1316-1325.**

[Abstract](#)

Risk of cancer in children and young adults conceived by assisted reproductive technology

Authors: Spaan M, et al.

Summary: Children conceived by ART did not have an increased risk of cancer in a nationwide historical cohort study of 24,269 children born from women treated with subfertility treatments between 1980 and 2001. A total of 231 cancers were observed in 47,690 live-born children after a median follow-up of 21 years. Overall cancer risk was not increased in children conceived by ART compared with children conceived naturally by subfertile women (HR 1.00; 95% CI 0.72–1.38) or compared with the standardised incidence ratio in the general population (1.11; 95% CI 0.90–1.36). Children conceived by ART had non-significant increases in the risks of lymphoblastic leukaemia (HR 2.44; 95% CI 0.81–7.37) and melanoma (HR 1.86; 95% CI 0.66–5.27) compared with children conceived naturally.

Comment: This is a very important study of more than 47,000 children over 21 years and found no increased likelihood of cancer in the children born after ART, compared to children conceived after low tech fertility interventions such as IUI or clomiphene and those conceived spontaneously. The strengths of this work are the size of the cohort, the length of time they have been followed and the meticulousness of Dutch reproductive research. This is also reassuring given that some groups have reported an increased risk of Beckwith-Wiedemann and Angelman syndromes in ART offspring which are linked with an increased risk of cancer.

Reference: *Hum Reprod.* 2019;**34(4):740-750.**

[Abstract](#)



Independent commentary by Dr Mary Birdsall,

BHB MB ChB Auckland; RANZCOG MSc (Oxon)

Dr Birdsall graduated from Auckland Medical School followed by post-graduate training at National Women's Hospital. She was awarded a Nuffield Scholarship and completed a Master's Degree in Human Reproduction at Oxford University. Mary is the Chair of Fertility Associates and works as a full time fertility specialist at Fertility Associates Auckland.

For full bio [CLICK HERE](#).

Pregnancy and neonatal outcomes of small follicle-derived blastocyst transfer in modified natural cycle in vitro fertilization

Authors: Teramoto S, et al.

Summary: The efficacy and safety of blastocyst transfer derived from small follicles (≤ 10 mm) and large follicles (≥ 11 mm) was compared in a retrospective cohort study in 1072 women who underwent frozen blastocyst transfer. There were no significant differences in the rate of chemical abortions (9.2% vs 10.9%), clinical abortions (12.2% vs 10.9%) and live births (43.8% vs 47.9%) for small follicle- and large follicle-derived blastocysts, respectively. Nor were there any significant differences in the incidence of abnormal karyotypes after spontaneous abortion or the incidence of major congenital abnormalities after live birth.

Comment: This interesting report found that embryos obtained from small follicles (defined as less than 10 mm) yielded blastocysts that were just as likely to make babies compared to blastocysts derived from larger follicles (11 mm or greater). The message for IVF doctors is to go into all follicles at egg collection and that a blastocyst should be assessed on its developmental and biopsy information and not on the size of the follicle from whence it came.

Reference: *Fertil Steril.* 2019;111(4):747-752.
[Abstract](#)

In vitro fertilization and autoimmunity

Authors: Di Rosa R, et al.

Summary: The prevalence of antiphospholipid antibodies was evaluated in 520 infertile women undergoing IVF. Positive auto-antibodies were detected in 19.2% of women and 6.7% met the classification criteria for systemic disease. Positive antiphospholipid antibodies were detected in 8.3% of women; 3.3% met the diagnostic criteria for antiphospholipid immune system disorders and 3.5% met criteria for other autoimmune disorders.

Comment: The usual indication for testing for autoimmune conditions in the reproductive world is when there is recurrent pregnancy loss or recurrent implantation failure. This report suggests that women with infertility may have a high prevalence of autoimmune disease. This may account for the increased pregnancy risks observed in women with infertility. It may be useful to consider screening for autoimmune conditions at the time of presentation with infertility.

Reference: *Eur J Obstet Gynecol Reprod Biol.* 2019;234:137-142.
[Abstract](#)

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FERTILITY ASSOCIATES NEWS CORNER



Introducing Dr Dean Morbeck

Ph.D., HCLD (ABB) MBA

Dr. Morbeck is currently the Scientific Director at Fertility Associates and an Honorary Lecturer in Obstetrics and Gynaecology at the University of Auckland. Prior to moving to NZ in 2016, Dean was an Associate Professor of Obstetrics and Gynecology and Laboratory Medicine and Pathology at the Mayo Clinic, USA. He has a keen interest in the quality of care provided to patients experiencing infertility, as evidenced by his publications on quality control, media composition and laboratory KPIs. He is actively involved with research, focusing on in vitro stress during embryo culture, specifically, identifying sources of stress and developing improved methods for detection and prevention of factors that cause stress during preimplantation embryo culture.

DEAN'S RECENT PUBLICATIONS:

- Human Reproduction 2019; 34 (1), 37-43. *Tracking quality: can embryology key performance indicators be used to identify clinically relevant shifts in pregnancy rate?*
DOI: [10.1093/humrep/dey349](https://doi.org/10.1093/humrep/dey349)
- Human Reproduction 2018; 33 (6), 991-997. *Should extended blastocyst culture include Day 7?* DOI: [10.1093/humrep/dey091](https://doi.org/10.1093/humrep/dey091)
- Human Reproduction Open 2017 (3) Issue 3, hox017. *Blastocyst culture in the Era of PGS and FreezeAlls: Is a 'C' a failing grade?*
DOI: [10.1093/hropen/hox017](https://doi.org/10.1093/hropen/hox017)

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The IVF-LUBE trial – a randomized trial to assess Lipiodol® uterine bathing effect in women with endometriosis or repeat implantation failure undergoing IVF

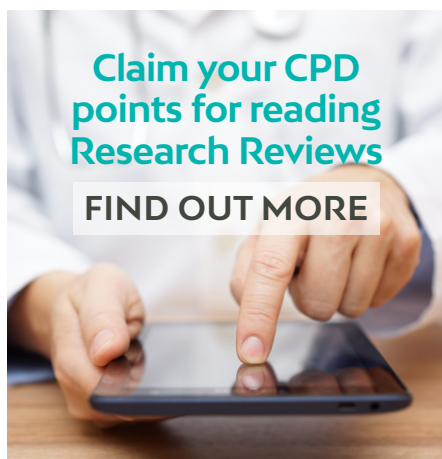
Authors: Reilly SJ, et al.

Summary: Uterine bathing with Lipiodol did not increase the success of IVF treatment in a randomised study of 70 women with endometriosis or repeat implantation failure. Live birth rates were 24% in women who received Lipiodol by hysterosalpingogram prior to IVF and 30% in women who received no intervention prior to IVF (RR 0.81; 95% CI 0.37–1.8). Live birth rates from pregnancies within 6 months were 33% and 32%, respectively (RR 1.03; 95% CI 0.53–2.0).

Comment: Lipiodol has been found to improve spontaneous conception in couples with unexplained infertility and in women with endometriosis. This study did not show an improvement in pregnancy rates in women with endometriosis or recurrent implantation failure prior to an IVF cycle. Lipiodol is also associated with an increased risk of thyroid dysfunction for several months after its use. Publication of negative trials is important otherwise there is a creep towards increasing numbers of unproven interventions being used by people who are desperate to conceive.

Reference: *Reprod Biomed Online.* 2019;38(3):380-386.

[Abstract](#)



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A randomized trial of progesterone in women with bleeding in early pregnancy

Authors: Coomarasamy A, et al.

Summary: Progesterone therapy did not improve pregnancy outcomes in a multicentre double-blind trial in 4153 women with vaginal bleeding in early pregnancy. Women were randomised to receive vaginal suppositories of progesterone 400 mg (n=2079) or placebo (n=2074) twice daily from the time they presented with bleeding through 16 weeks of gestation. The live birth rate (gestational age ≥ 34 weeks) was 75% in the progesterone group and 72% in the placebo group (relative rate 1.03; 95% CI 1.00–1.07; p=0.08).

Comment: Progesterone levels have been observed to be lower in pregnancies that are destined to fail and hence this is the basis of the desire to supplement progesterone levels to salvage a pregnancy. This very large study showed that progesterone supplementation at the time of a threatened miscarriage and continuing until 16 weeks did not improve the chances of a live birth. The one group who did appear to benefit from progesterone supplementation after bleeding were those women with recurrent pregnancy loss. 98/137 (72%) women with 3 or more miscarriages given progesterone had live births compared to 85/148 (57%) who were given a placebo (relative rate 1.28; 95% CI 1.08–1.51).

Reference: *N Engl J Med.* 2019;380(19):1815-1824.

[Abstract](#)

Marijuana smoking and markers of testicular function among men from a fertility centre

Authors: Nassan FL, et al.

Summary: Marijuana smoking had no deleterious effect on testicular function in a longitudinal study of 662 subfertile men. Sperm concentrations were significantly higher in 365 men who had ever smoked marijuana than in 297 men who had never smoked marijuana (62.7 million/mL vs 45.4 million/mL; p=0.0003). Total sperm counts were also higher in men who had ever smoked marijuana compared with never smokers. There were no significant differences in sperm concentrations or total sperm counts between current and past marijuana smokers. No associations were detected between marijuana smoking and other semen parameters, markers of sperm DNA, or reproductive hormones except for FSH concentrations, which were significantly lower in marijuana smokers.

Comment: We have always been taught that marijuana smoking had a detrimental effect on sperm quality and we should be advising couples trying to conceive to stop smoking dope. A recent Danish study showed a 28% reduction in sperm counts in healthy military recruits who smoked at least once per week. This study reported higher sperm concentrations and lower FSH levels in men who had smoked marijuana at any time in their lives compared to the never users. There were no differences in the men who currently smoked vs those who had been past smokers. The major criticism of this study is that the men self-reported but nevertheless I don't think we can continue to be so dictatorial about dope and maybe it is OK to inhale.

Reference: *Hum Reprod.* 2019;34(4):715-723.

[Abstract](#)

Rotating night shift work and menopausal age

Authors: Stock D, et al.

Summary: The association between cumulative and current rotating night shift work and age at natural menopause was assessed in a cohort of 80,840 women enrolled in the Nurse's Health Study 2. Over 22 years of follow-up, 34% of women reached natural menopause. An increased risk of earlier menopause was observed in women who worked ≥ 20 months of rotating night shifts in the previous 2 years compared with women who did not work rotating night shifts (HR 1.09; 95% CI 1.02–1.16). An increased risk of earlier menopause was also observed in women who worked ≥ 10 years of cumulative rotating night shifts.

Comment: Working night shifts has been found to be associated with a number of adverse health outcomes such as obesity, depression, workplace injuries, breast cancer and heart disease. This study is part of the large Nurse's Health Study and showed that nurses who worked some night shifts and some day shifts had an earlier menopause. Yet another reason to try and have a day job.

Reference: *Hum Reprod.* 2019;34(3):539-548.

[Abstract](#)

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