

Fertility RESEARCH REVIEW™

Making Education Easy

Issue 32 – 2022

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Abbreviations used in this issue

ART = assisted reproductive technology
ERA = endometrial receptivity array
IVF = in vitro fertilisation
OI/UII = ovulation induction/intrauterine insemination
OR = odds ratio
PGT-A = preimplantation genetic testing for aneuploidy
PRP = platelet-rich plasma
SART = Society for Assisted Reproductive Technology



PHARMACY GUILD
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Welcome to the latest issue of Fertility Research Review.

In this issue, a cost-effectiveness analysis evaluates planned oocyte cryopreservation as a strategy for delayed childbearing compared with IVF + PGT-A at advanced reproductive age, a Chinese cohort study demonstrates an association between the vaginal microbiome and female fecundability, and a Swedish study finds evidence of significant endometriosis in approximately one-fifth of women about to undergo ART (76% of whom were unaware they had it). Also in this issue, an Australian cohort study reports a big increase in the number of babies born with the use of fertility treatment, and a UK study shows that time-lapse embryo incubators are better than standard benchtop incubators.

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

Kind regards,

Dr Mary Birdsall

marybirdsall@researchreview.co.nz

A SART data cost-effectiveness analysis of planned oocyte cryopreservation versus in vitro fertilization with preimplantation genetic testing for aneuploidy considering ideal family size

Authors: Bakkensen JB et al.

Summary: This US study investigated the cost effectiveness of planned oocyte cryopreservation (OC) as a strategy for delayed childbearing compared with IVF/PGT-A at advanced reproductive age. Data were extracted from the SART database and other clinical sources to develop a simulated cohort of patients desiring delayed childbearing with an ideal family size of one or two children. Analysis of the data showed that, for those desiring one live birth, planned OC at age 33 with warming at age 43 decreased the mean total cost per patient from \$US62,308 to \$US30,333 and increased the likelihood of live birth from 50% to 73% compared with no OC with up to 3 cycles of IVF/PGT-A at age 43. For those desiring two live births, two cycles of OC at age 33 and warming at age 40 yielded the lowest cost per patient and the highest likelihood of having two children (\$US51,250 and 77%, respectively) when compared with pursuing only one cycle of OC (\$US75,373 and 61%), no OC and IVF/PGT-A with embryo banking (\$US79,728 and 48%), or no OC and IVF/PGT-A without embryo banking (\$US79,057 and 19%).

Comment: In my humble opinion this is the most important article in this issue. The authors looked at the huge SART database and modelled that if a woman wants one child, she is better to do egg freezing before she is 32 rather than three cycles of IVF at age 43, and if she would like two children, she should do two cycles of egg freezing at age 31 or earlier. Egg freezing is the cheaper option and more likely to result in a live birth or two. The strengths of this study are the inclusion of two live births not just one (as most women view a family as more than one child), the use of real user-pays costs across the US, the inclusion in the model of starting to try for a pregnancy at age 40, the use of PGT-A, and the size of the SART database. IVF clinicians are frequently asked if women should egg freeze or wait for a partner to appear and I think these data provide useful information for those conversations.

Reference: *Fertil Steril* 2022;118(5):875-84

[Abstract](#)

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The association between the pre-pregnancy vaginal microbiome and time-to-pregnancy

Authors: Hong X et al.

Summary: This Chinese cohort study evaluated the impact of the vaginal microbiome on the fecundability of women planning pregnancy. Pre-pregnancy vaginal swabs were taken from women participating in the Free Pre-Pregnancy Health Examination Project from Jun–Oct 2018 (n=89, phase I) and from Nov 2018 to May 2020 (n=389, phase II). 59.6% of women in phase I became pregnant within a year. Pre-pregnancy vaginal microbial community structures of the pregnant and non-pregnant groups differed significantly. The abundance of the genus *Lactobacillus* was higher in the pregnant group than the non-pregnant group, and the abundance of the genus *Gardnerella* was higher in the non-pregnant group than the pregnant group. In phase II, female fecundability increased with higher absolute loads of *L. gasseri* but decreased with higher absolute loads of *Fannyhessea vaginae*. Clustering analysis showed that a vaginal microbiome characterised by a higher abundance of *L. iners* and a lower abundance of *L. crispatus* and *L. gasseri* was associated with a 55% reduction in fecundability compared with a vaginal microbiome featuring three *Lactobacillus* species and low abundance of *G. vaginalis* and *F. vaginae*.

Comment: The body's microbiome is the new cool organ system to study and this report on the vaginal microbiome provides an interesting read. This study from China (which is pertinent as vaginal microbiomes differ from country to country) shows that certain *Lactobacilli* were associated with a higher chance of spontaneous pregnancy. However, the study was not controlled for semen quality, needed more numbers, and did not standardise for when in the menstrual cycle the swabs were taken as menstruation causes a significant shift in vaginal microflora. I think much more work is required before we will be recommending interventions to alter the vaginal flora, but watch this space.

Reference: *BMC Med* 2022;20(1):246
[Abstract](#)

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Systematic review of subsequent pregnancy outcomes in couples with parental abnormal chromosomal karyotypes and recurrent pregnancy loss

Authors: Li S et al.

Summary: This systematic review and meta-analysis investigated pregnancy outcomes among couples with recurrent pregnancy loss (RPL) and abnormal parental karyotypes. A search of various databases identified 11 studies that reported pregnancy outcomes in 6301 couples with RPL. Meta-analysis of the data showed that couples with RPL with abnormal karyotypes had a significantly lower first pregnancy live birth rate than those with a normal karyotype (58.5% vs 71.9%; OR 0.55, 95% CI 0.46–0.65). The differences in accumulated live birth rates were not significant, but the miscarriage rate was higher in couples with RPL and abnormal karyotypes (53.0% vs 34.7%; OR 2.21, 95% CI 1.69–2.89). In couples with RPL and abnormal karyotypes, preimplantation genetic diagnosis (PGD) did not increase the accumulated live birth rate but markedly reduced the miscarriage rate compared with expectant management.

Comment: Before PGD was invented, couples where one partner had an abnormal karyotype and RPL were advised to continue to try to conceive because they would likely achieve their desired number of liveborn children if they were sufficiently resilient to go through more pregnancy losses. PGD then became part of clinical practice and many clinicians and would-be parents chose this as their pathway of choice. This report suggests that either PGD or spontaneous conception is reasonable and results in the same number of children, with the PGD option resulting in fewer miscarriages. A caveat that I would add is that this only applies to couples who conceive easily and have the luxury of time, whereas if a couple conceives rarely and where the woman is older, then PGD may be a better option.

Reference: *Fertil Steril* 2022;118(5):906-14

[Abstract](#)

Prevalence of endometrioma and deep infiltrating endometriosis at transvaginal ultrasound examination of subfertile women undergoing assisted reproductive treatment

Authors: Alison S et al.

Summary: This cross-sectional study estimated the prevalence of endometriosis in women with subfertility who were due to undergo ART. 1191 women aged 25–39 years who had been accepted for their first ART underwent a systematic transvaginal ultrasound examination. The prevalence of endometriosis was 21.8%. Overall, 10.5% of women had endometrioma and 17.2% had deep infiltrating endometriosis. 75.8% of women with endometriosis had not been diagnosed previously. The most common locations for endometriotic lesions were the uterosacral ligaments and the ovaries.

Comment: This Swedish study performed a high-resolution ultrasound on women about to start IVF treatment and found evidence of significant endometriosis in 22%, of whom 76% did not know they had it. This study made me think that all IVF clinicians need to upskill their ultrasound technique and get better ultrasound gadgetry. Women want to know whether they have endometriosis so they may make informed decisions about the management of this disease, so they do not have to put up with significant symptoms, and in NZ so they may accumulate more points towards publically funded fertility treatment, but mostly because people want a reason as to why they are struggling to conceive. Fertility clinicians need to lift their ultrasound game.

Reference: *Fertil Steril* 2022;118(5):915-23

[Abstract](#)

Population-wide contribution of medically assisted reproductive technologies to overall births in Australia: Temporal trends and parental characteristics

Authors: Choi SKY et al.

Summary: This population-based Australian birth cohort study determined trends in the contribution of medically-assisted reproduction (MAR) technologies to overall births over time. 898,084 births (606,488 mothers) in New South Wales and the Australian Capital Territory in 2009–2017 were analysed. The proportion of MAR births increased from 5.1% in 2009 to 6.7% in 2017. The proportion of OI/IUI births remained stable at around 2% of all births (32% of all MAR births); births conceived using clomiphene citrate decreased whereas births conceived using letrozole increased. ART births conceived by frozen embryo-transfer increased nearly 3-fold over the study period. Overall, there was a 55% increase in the number of ART-conceived births from 2009 to 2017. Interestingly, 17.6% of births to mothers aged ≥40 years were conceived using ART treatment in 2017. ART children (but not OI/IUI children) were more likely than naturally-conceived children to have parents who were socioeconomically advantaged.

Comment: This large observational dataset shows the big increase in numbers of babies being born with the use of fertility treatment, and it now contributes to nearly 7% of all births in Australia. These births are more likely to occur to women who were born in Australia, live in cities or in areas of advantaged neighbourhoods. This paper highlights the inequities in Australia in terms of who accesses the highly subsidised IVF programme and I think there should be some efforts made to ensure all women have access to funded IVF.

Reference: *Hum Reprod* 2022;37(5):1047-58

[Abstract](#)

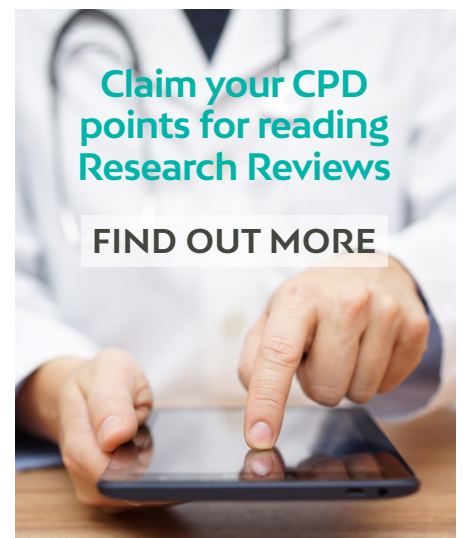
Independent commentary by Dr Mary Birdsall, BHB MB ChB Auckland; FRANZCOG MSc (Oxon)

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 prior Chair and Group Medical Director of Fertility Associates and until recently worked as a fertility specialist at Fertility Associates Auckland. She has a special interest in fertility preservation and lifestyle influences on fertility. Mary is a previous member of the Ethics Committee for Assisted Reproductive Technology and is the editor of the book "Making Babies".



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The impact of an endometrial receptivity array on personalizing embryo transfer for patients with infertility

Authors: Tran HP et al.

Summary: This meta-analysis investigated the effectiveness of the ERA test on IVF outcomes. A search of PubMed/MEDLINE, ScienceDirect, and Scopus databases identified 17 studies (4 randomised controlled trials and 13 cohort studies) involving 7052 patients that were suitable for inclusion. Meta-analysis of the data showed that personalised embryo transfer (PET) on the basis of ERA did not optimise gestational outcomes (implantation rate, clinical pregnancy rate, ongoing pregnancy rate, or miscarriage rate). Subgroup analysis revealed that women undergoing PET in their first IVF cycle had an increased live birth rate (risk ratio 1.24, 95% CI 1.03–1.49).

Comment: This is a meticulous meta-analysis of the ERA assay and suggests that it is not useful in terms of live births except possibly in a first cycle. The first cycle data were based on only two studies. It is very hard to withdraw options and as IVF clinicians we are very good at adding extra measures in. I think it is important that we critically evaluate our add-ons. ERA costs our patients financially, there are small risks to the procedure, it takes away a further month in their reproductive lives and most importantly is probably not beneficial. Is this the end of the ERA era?

Reference: *F S Rev* 2022;3(3):157-73

[Abstract](#)

Progesterone supplementation in natural cycles improves live birth rates after embryo transfer of frozen-thawed embryos

Authors: Wånggren K et al.

Summary: This Swedish trial investigated whether vaginal progesterone supplementation after frozen-thawed embryo transfer in natural cycles improves the live birth rate. 488 women receiving embryo transfer in natural cycles were randomised to receive supplementation with progesterone vaginal tablets (100mg twice daily) starting from the day of embryo transfer, or no supplementation. 34.8% of women in the progesterone-supplemented group and 24.1% of controls had a live birth (OR 1.635, 95% CI 1.102–2.428; p=0.017).

Comment: This randomised controlled study in women doing natural thaw cycles shows a better live birth rate when progesterone supplementation was used compared to no exogenous progesterone. There is good evidence that natural cycles result in improved perinatal outcomes presumably because of the presence of a functioning corpus luteum. I think there needs to be more work to determine whether there are any differences in perinatal outcomes in natural cycles versus progesterone-supplemented natural cycles. I would also advocate for further work to improve the progesterone products because most women find the progesterone suppositories messy and unpleasant and progesterone injections painful.

Reference: *Hum Reprod* 2022;37(10):2366-74

[Abstract](#)



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Incubator type affects human blastocyst formation and embryo metabolism

Authors: Kermack AJ et al.

Summary: This prospective trial investigated whether the type of incubator used to culture human preimplantation embryos affects development to the blastocyst stage and embryo metabolism. 585 sibling embryos were randomised to either the time-lapse system (TLS; 289 embryos) or the standard benchtop incubator (296 embryos) over a 23-month period in a UK University Hospital Fertility Clinic. Overall, blastocyst formation rate on day 5 was significantly higher in embryos cultured in the TLS than in the standard incubator (55% vs 45%; $p=0.013$), and there were more blastocysts suitable for cryopreservation in the TLS (31% vs 23%; $p=0.032$). Embryos cultured in the TLS had increased total amino acid utilisation ($p<0.001$) and reduced amino acid production ($p<0.001$) than those cultured in the standard incubator.

Comment: This study shows that embryos cultured in time-lapse incubators were more likely to develop into blastocysts, were more likely to be frozen, were just as likely to result in an ongoing pregnancy, and utilised amino acids differently when compared to embryos cultured in a standard benchtop incubator. Embryos cultured in a benchtop incubator need to be removed in order to check on their development and are exposed to the light, temperature and gas change along with movement. I think that time-lapse incubators are the way forward.

Reference: *Hum Reprod* 2022; published online Oct 26

[Abstract](#)

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Determinants of transplantation success with cryopreserved ovarian tissue: Data from 196 women of the FertiPROTEKT network

Authors: Lotz L et al.

Summary: This registry study determined pregnancy and live birth rates after ovarian tissue transplantation. 196 women who underwent a total of 244 ovarian tissue transplantations at 26 FertiPROTEKT network centres in 2007–2019 were followed up through till Dec 2020. Mean age was 31.3 years at the time of tissue cryopreservation and 35.9 years at the time of transplantation. The pregnancy rate was 30.6% per first transplantation and 32.7% per patient. It was higher after first transplantation than after second and subsequent transplantations (11.8%). Live birth rate was 25.0% per first transplantation and 26.5% per patient (28.2% in women aged <35 years and 16.7% in women over 35). Pregnancy rates after first transplantation were higher in centres that had performed at least ten transplantations than centres that had performed fewer than ten transplantations (35.1% vs 25.4%; $p=0.12$).

Comment: Ovarian transplantation is now deemed by the American Society for Reproductive Medicine to be a safe and clinically acceptable treatment. This report tells us that the first transplant is more likely to be successful than subsequent transplants, that centres with more expertise get better results, that ovaries frozen at a younger age do better, and that radiotherapy to the pelvis makes pregnancy less likely. All of these findings are expected but it is really good to see some outcome data being published.

Reference: *Hum Reprod* 2022; published online Oct 22

[Abstract](#)

An audit of clinical outcomes following ovarian administration of platelet-rich plasma (PRP) in women with severe diminished ovarian reserve

Authors: Tremellen K & Pacella-Ince L

Summary: This study investigated the effects of ovarian PRP treatment on IVF and pregnancy outcomes in women with severe diminished ovarian reserve and previous IVF treatment failure. 20 consecutive women aged <45 years who were undergoing ovarian PRP treatment were included in the analysis. PRP treatment had no significant effect on oocyte number, but increased the number of embryos generated compared to patients' own pre-PRP IVF cycle (0 vs 2 embryos; $p=0.005$). Four patients conceived viable, genetically normal pregnancies in their next IVF cycle, and a further two conceived naturally in the four months after PRP treatment. Five of these pregnancies were in women aged ≥ 40 years.

Comment: The holy grail of the IVF world remains helping women in their 40s with very poor ovarian reserve have their own genetic children. This study is a small case series where the women's own blood was used to produce PRP and this was then injected into the ovaries under ultrasound guidance and then an IVF cycle was performed 2 months later. I am always highly critical when previous failed treatment is used as the control however if we view this as a case series then the outcomes look interesting, with 6/18 women having ongoing pregnancies with no miscarriages and more embryos being created. I do think that this needs further study before recommending PRP as being yet another add-on.

Reference: *ANZJOG* 2022;62(5):767-72

[Abstract](#)

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