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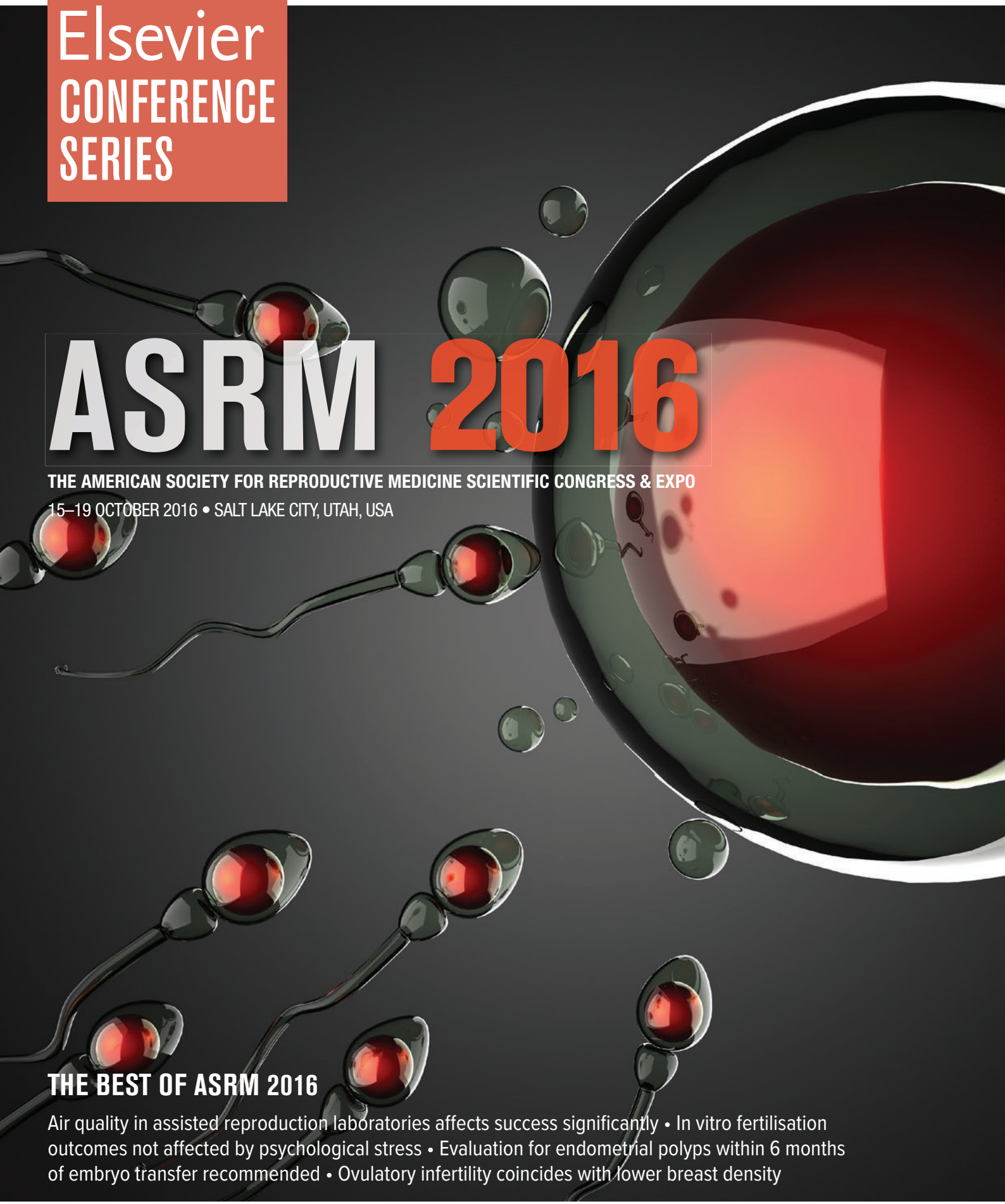

ASRM 2016

THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE SCIENTIFIC CONGRESS & EXPO

15–19 OCTOBER 2016 • SALT LAKE CITY, UTAH, USA

THE BEST OF ASRM 2016

Air quality in assisted reproduction laboratories affects success significantly • In vitro fertilisation outcomes not affected by psychological stress • Evaluation for endometrial polyps within 6 months of embryo transfer recommended • Ovulatory infertility coincides with lower breast density

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Overheard at **ASRM**...

Many women trying to conceive use personal lubricants, but these may be toxic to sperm

"It appears that the popularity of personal lubricants is increasing and there are significant numbers of women using them who are actively trying to conceive. We need to make patients aware that their choice of lubricant may affect their chances of becoming pregnant."

Owen K. Davis, MD, President of ASRM, commenting on

- O-196 I. Molina et al. *Sperm survival assay for toxicity evaluation in ultrasound gels and vaginal lubricants used in reproductive medicine*
- P-481 S. Johnson et al. *Vaginal lubricant use among women trying to conceive: insights from a survey of over 1000 participants*

First baby born using spindle nuclear transfer to prevent mitochondrial disease

"This work represents an important advancement in reproductive medicine. Mitochondrial disease has been an important and challenging problem. If subsequent research determines the safety and efficacy of spindle nuclear transfer, we look forward to it being an option for patients who risk transmitting mitochondrial diseases to their children."

Owen K. Davis MD, President of ASRM, commenting on

- O-267 Zhang, et al. *First live birth using human oocytes reconstituted by spindle nuclear transfer for mitochondrial DNA mutation causing Leigh syndrome*

BRCA-positive patients fare well using IVF with PGD

"It is gratifying that BRCA-mutated patients do so well with ART including PGD, especially if they are not affected by an infertility diagnosis. They have an excellent chance of having a child and avoiding transmitting the BRCA gene to their child."

Richard Paulson, MD, President-elect of ASRM commenting on

- P-56 S. Rechitsky et al. *Reproductive outcome of 128 PGD cycles for breast cancer*
- P-704 L. Sekhon et al. *Ovarian reserve and embryonic aneuploidy rates in BRCA 1 and 2 carriers*
- P-710 A. King et al. *Excellent embryo development and IVF outcomes for patients with germline BRCA1 and BRCA2 mutations*

Reproductively, endocrine disrupting chemicals are bad news

"Endocrine disrupting chemicals in the environment are one of the most insidious threats to human (and animal) reproductive health. As the Rochester study demonstrates, most people in the US, even those with a high degree of health literacy, do not have adequate knowledge of the dangers of these substances and how to avoid them. Until BPA, phthalates and other endocrine disruptors can be replaced in industry with safer chemicals, we need to educate patients from a young age to avoid them in their environment."

Owen K. Davis, MD, President of ASRM, commenting on

- O-1 C. Messerlian et al. *Maternal and paternal preconception phthalate exposure and birthweight of IVF singletons*
- O-2 Q. Yang et al. *Early life developmental exposure to endocrine disrupting chemicals increases the risk of adult onset of uterine fibroids by permanently reprograming the epigenome of myometrial stem cells towards a pro-fibroid landscape*
- P-472 A. Pilato et al. *Knowledge, attitudes, and behaviors related to environmental chemical exposure among women seeking fertility care*

Chemicals in women's diet affect IVF success

"A state of good health, including a healthy diet is essential to IVF success. We need to educate our patients on pesticides and sweeteners. Cutting out diet soda, sweeteners and sugar, and learning about the USDA's pesticide classifications to be able to shop smarter may take some effort, but patients need to know they can improve their chances of pregnancy if they take these steps."

Owen K. Davis, MD, President of ASRM, commenting on

- O-67 Y. Chiu et al. *Fruit and vegetable intake and their pesticide residues in relation to outcomes of assisted reproductive technology.*
- P-420 G. Halpern et al. *Artificial sweeteners – do they bear an infertility risk?*

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Reaching new heights in reproductive medicine

Welcome to our special coverage of the American Society for Reproductive Medicine 2016 Scientific Congress and Expo, part of the Elsevier Conference Series that aims to bring you key clinical and scientific news from the world's top medical congresses..

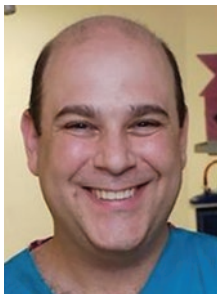
This special ASRM2016 issue, kindly brought to you through advertising by Ferring Pharmaceuticals Australia, brings together leading research from the top guns in reproductive medicine to tackle the puzzles of reproductive medicine. Our Elsevier Australia news team has independently reported from the 1000 presentations on offer at ASRM 2016 to bring you the best ASRM has to offer.

Topics include long-acting reversible contraceptives, genomic imprinting (epigenetics) in health and disease, regenerative therapies to treat infertility, embryogenesis success determined by environment, psychological stress on IVF success, the reproductive health needs of cancer survivors; and emerging research in contraception.

We hope you enjoy this issue of the Elsevier Conference Series.

Anne Neilson
Managing Editor
Elsevier Conference Series

Air quality in assisted reproduction laboratories affects success significantly



STEVEN PALTER

Blastocyst conversion and implantation rates and ongoing pregnancy rates were higher when comprehensive removal and control of airborne pathogens were undertaken in the in vitro fertilisation laboratory.

Steven Palter, MD, of Gold Coast In Vitro Fertilization, Woodbury, New York, presented this outcome of a multicentre, retrospective evaluation of a proprietary air purification system.

He explained that successful preimplantation embryogenesis and the reproductive potential of the human embryo depend on a number of variables including the changing organic chemistry of the ambient air within the in vitro fertilisation laboratory.

Ambient air carries dynamic levels of embryotoxic volatile organic compounds and viable particulates. These compounds and particulates play a critical role in preimplantation toxicology and in the influence of ambient air on epigenesis.

Dr Palter and coinvestigators conducted the largest cohort study to date to evaluate a proprietary air purification system in its reduction of airborne pathogens. The system is designed to comprehensively remediate airborne embryotoxic pathogens using targeted engineered molecular media and genomically modelled biological inactivation.

These multimedia air filtration and inactivation systems address airborne threats often overlooked in a laboratory environment. Seemingly innocuous and unrelated factors outside the laboratory can be harmful to embryos that enter the clinical and laboratory space.

Contaminants outside the lab from road construction, vehicle exhaust, or pesticides can permeate the space and disrupt embryogenesis. Volatile organic compounds from cleaning supplies, rubbing alcohol, colognes, and hand sanitisers are often brought into the lab by laboratory and clinical personnel.

Dr Palter and colleagues quantified embryogenesis and patient outcomes in multiple in vitro fertilisation programs where the system is employed.

“Millions of years of biology,” he said, “have evolved to protect a fragile growing embryo. In vitro fertilisation has undergone incredible advances but has not been able to meet the challenge of invisible toxins dissolved in air that fragile embryos cannot defend against.”

He continued, “We were the third centre in the world to install a unique system that, for the first time, completely eliminates all known bacteria, fungi, particulates, and invisible toxic volatile organic compounds.

“This study, the largest of air purification and in vitro fertilisation, was an attempt to verify the impact of the system.”

Over a 24- to 48-month period, clinical outcome data from all nondonor patients who underwent in vitro fertilisation (n = 5319) in nine independent in vitro fertilisation programs was evaluated. A total of 2761 patients cycled in an environment protected by preexisting mechanisms of air filtration and 2558

patients after installation of the air purification system.

Blastocyst conversion rate was defined by zygotes reaching the blastocyst stage by day 5. The implantation rate was delineated by these criteria:

- Positive fetal cardiac activity per transferred embryo
- Ongoing pregnancy by positive fetal cardiac activity
- Loss rate as an intrauterine gestational sac without subsequent fetal cardiac activity.

Differences in patient demographics, program, and pre- and postinstallation variables were evaluated by multivariate analyses. Statistical analyses included odds ratios calculated with 95% confidence intervals and P = 0.05.

After installation of the air purification system, cultured embryos exhibited a significant increase in the rates of blastocyst conversion (33.7% vs 54.4%, P = 0.0001) and implantation (29.7% vs 41.4%, P = 0.0001); as well as ongoing pregnancy (42.7% vs 57.6%, P = 0.0001) from all maternal ages, pre- and post- air purification system, respectively.

Embryos cultured amid the air purification system-controlled environment exhibited a significant decrease in loss rate (27.7% vs 20.3%; P = 0.0001). Multivariate analysis showed that other variables were not significant.

Dr Palter concluded that comprehensive removal and control of airborne pathogens within the in vitro culture environment were associated with a statistically significant increase in the blastocyst conversion rate, implantation rate, ongoing pregnancy, and a decrease in the rate of loss.

“Just as we need clean, pure air to survive,” he added, “so do human embryos. The study showed that embryos outside the body in the in vitro fertilisation lab are exquisitely affected by even microscopic traces of contaminants. A new, comprehensive air purification system can protect these tiny embryos from invisible toxins, and this protection leads to better outcomes.”

“Since the impact was so large and significant,” he asserted, “the study demonstrates that comprehensive air purification helps ensure maximal pregnancy outcomes of in vitro fertilisation.”

Blastocyst quality the most important predictor of live birth in women 40–43 years who receive blastocyst transfer

Elective single blastocyst transfer should be expanded to women older than 39 years since, in women 40–43 years of age, when a blastocyst is obtained, age does not predict live birth.

Samer Tannus, MD, of McGill University, Montreal, Quebec, Canada, and coinvestigators sought to evaluate prognostic factors for live birth in fresh blastocyst transfer cycles in women of advanced age, in this retrospective cohort study.

Women age 40–43 years who underwent fresh, nondonor blastocyst transfer between 2011 and 2015 were analysed. Embryos were cultured to the blastocyst stage and transferred on the fifth day. Territorial law allows a maximum of two blastocysts to be transferred to women in this age group. Women were excluded if they had undergone more than three cycles of in vitro fertilisation.

Logistic regression analysis of baseline demographic characteristics and ovarian stimulation parameters was performed to determine predictors of live birth.

The analysis included 348 women who underwent 387 fresh blastocyst transfer cycles. A mean of 1.4 ± 0.5 blastocysts were transferred. Twenty-three percent achieved live birth, 8% multiple birth. After logistic regression analysis, women who experienced live birth were found to be more likely to exhibit:

- transferring fully expanded vs early blastocysts, odds ratio 2.8 (95% CI 1.18–7.38, P = 0.016)
- transferring two vs one blastocyst, odds ratio 1.88 (95% CI 1.08–3.06, P = 0.02)
- using lower dose of gonadotropins, odds ratio 0.99 (95% CI 0.99–0.99, P = 0.003)
- younger age, odds ratio 0.68 (95% CI 0.49–0.93, P = 0.017).

The following factors did not predict live birth:

- day 3 level of follicle-stimulating hormone (7.4 ± 2.4 vs 7.9 ± 4.2 IU/L)
- antral follicle count (13.6 ± 9.4 vs 11.9 ± 9.7)
- number of oocytes collected (12 vs 11).

Transferring two blastocysts rather than one was associated with an increased chance of multiple birth (16.6% vs 0%, P = 0.008), but not of live birth.

Dr Tannus concluded, “In women 40–43 years of age undergoing fresh blastocyst transfer, ovarian response to stimulation as reflected by a lower total dose of needed gonadotropins, blastocyst quality, and the transferal of two blastocysts were found to be the best predictors of live birth.

“Importantly,” he noted, “the number of blastocysts transferred increased both the live and multiple birth rates. This association suggests that the practice of elective single blastocyst transfer should be expanded to women above the age of 39 years.”

He added, “Among women 40–43 years of age, it would be optimal to decrease the incidence of multiple births, as these are associated with increased complications in advanced maternal age. If pregnancy doesn’t occur, subsequent frozen-warmed embryo transfer can be performed.”

Egg cell donors aged 21–23 and 28–31 years produce comparable numbers of oocytes and blastocysts

Outcomes of in vitro fertilisation do not vary with oocyte donor aged 21–23 versus 28–31 years. Donors in the younger age group produced a comparable number of oocyte and blastocysts as those aged 28–31 years.

This conclusion is based on results of a retrospective cohort study presented by Meghan Pierce, RN, of Reproductive Medicine Associates of New Jersey, Basking Ridge, who undertook the study because infertile patients in her centre often expect that young oocyte donors will provide a better outcome.

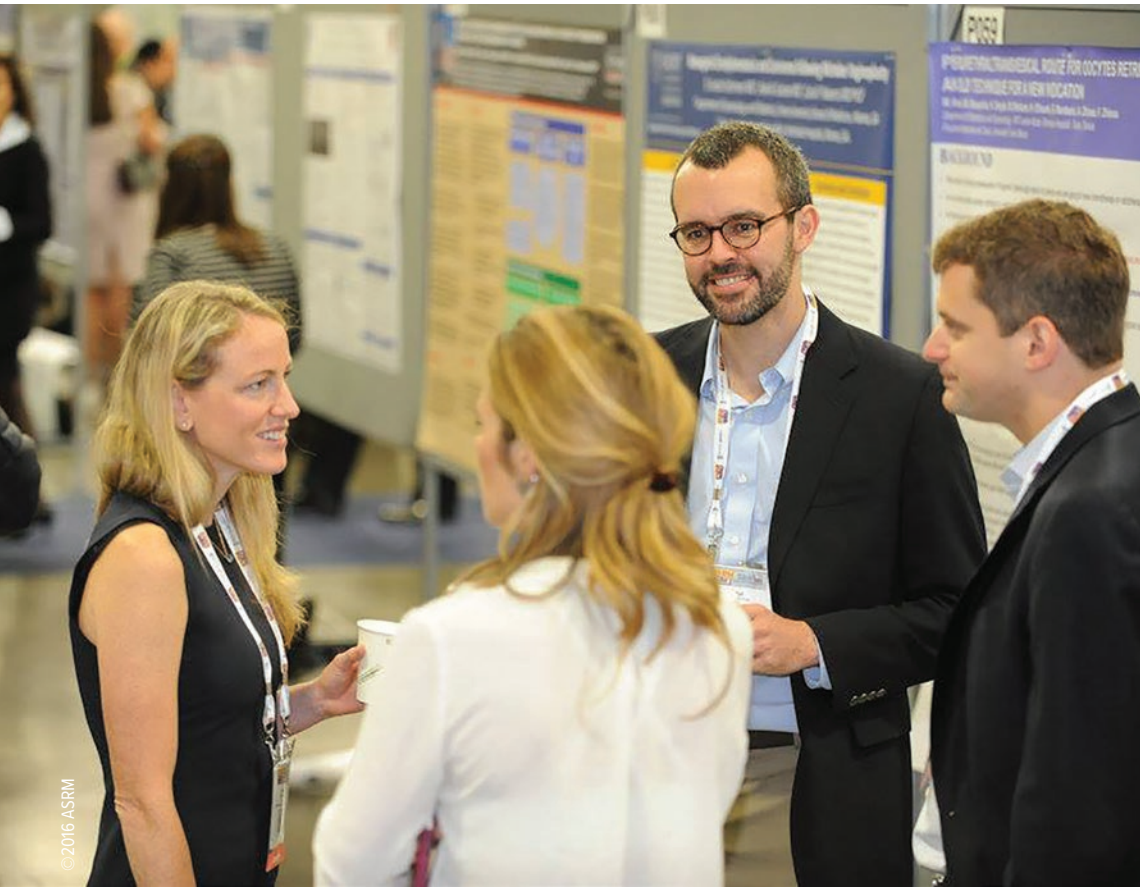
So Ms Pierce and coinvestigators set out to compare oocyte donors aged 21–23 versus 28–31 years to ascertain whether the younger oocyte donors prove better cycle outcomes than the older oocyte donors.

"As the manager of nursing and clinical services education at Reproductive Medicine Associates of New Jersey," she said, "I noticed many of our recipients were requesting that we use eggs from donors aged 21–23 years, even after we explained that eggs from 'older' donors are equally effective. I wanted to educate our recipients using data. I thought I could use such information to reassure them about proceeding with any donor who has been screened by our practice."

A total of 485 patients electronic medical records from 2011 to 2016 were analysed. Only the initial oocyte donor cycle was included. Group A donor age was 21–23 years and Group B, 28–31 years. Per protocol, women with an anti-Mullerian hormone level <1.2 ng/mL and antral follicle counts <12 were excluded.

Ovarian stimulation of oocyte donors employed antagonist or Lupron down-regulation protocol and transvaginal ultrasound-guided aspiration. Intracytoplasmic sperm were injected on M2 oocytes and embryos cultured to the blastocyst stage.

The total number of oocytes retrieved, total number of blastocysts, aneuploidy rate, and recipient ongoing pregnancy rates were analysed. Statistical analysis was performed using Student's t-test or chi square where applicable. Multivariable logistic regression was performed to account for possible confounding.



The two groups exhibited no significant difference in baseline anti-Mullerian hormone or antral follicle counts. Likewise, the number of oocytes retrieved and blastocysts obtained were similar between groups. Ongoing pregnancy rates did not differ (72.6% vs 69.1%).

Ms Pierce concluded that the success of in vitro fertilisation is not affected by extremes of oocyte donor age. Donors aged 21–23 years produce a comparable number of egg cells and blastocysts as those aged 28–31 years. Moreover, the two groups experience comparable pregnancy and aneuploidy rates. ■

Home-based ultrasound monitoring effective, feasible for in-cycle monitoring of women undergoing in vitro fertilisation

NINA RESETKOVA

Home-based self-operated endovaginal telemonitoring has been shown to compare well with clinic-based monitoring.

Nina Resetkova, MD, MBA, of Boston IVF, Waltham, Massachusetts, reported this outcome of a prospective feasibility study explaining, "We sought to assess the feasibility of home-based, self-operated endovaginal telemonitoring in women undergoing controlled ovarian stimulation with gonadotropins for in vitro fertilisation. We compared the home-based system with facility-based testing."

Six women engaged in home-based, self-operated endovaginal telemonitoring in parallel with standard-of-care, clinic-based ultrasound monitoring of follicle maturation. They underwent 1 hour of instruction on the use and functionality of the home ultrasound monitoring kit. All were deemed competent on use of the system.

The women conducted home-based ultrasonography every day, from stimulation through to the day before oocyte retrieval. The images they acquired were transmitted electronically to staffers. At the conclusion of cycle monitoring, the images were compared and the women evaluated their experience via survey.

Follicle size between home and clinic ultrasonography was compared for each day the women underwent clinic-based monitoring. The correlation coefficient between the 68 direct-pair follicle size comparisons was 0.92. Each woman emailed staffers an average of eight times over the cycle.

The decision to trigger would have occurred on the same cycle day in all participants when two or more 18-mm lead follicles were used as the minimum trigger criterion. Home-based monitoring would have led to a preferred trigger day in one woman.

If only home-based monitoring were used, an estimated 5.5 hours would have been saved per patient, including about 60–70 minutes of total driving time.

Dr Resetkova concluded, "The images we obtained by home-based, self-operated endovaginal telemonitoring correlated well with clinic-based ultrasonography. The critical decision to administer a trigger injection compared well with clinic-based ultrasound. And the women were highly satisfied according to their responses on objective and subjective measures."

In the second phase of the study, self-operated endovaginal telemonitored imaging is replacing routine clinic-based monitoring throughout a cycle. Dr Resetkova and colleagues are looking to minimise the time burden and inconvenience of conventional in-cycle monitoring.

Retrieval of larger oocyte cohorts maximises the number of children born per cycle of in vitro fertilisation

KEVIN S. RICHTER

In women undergoing in vitro fertilisation, more retrieved oocytes lead to higher numbers of vitrified embryos and ultimately higher live births per retrieval event.

This outcome of a retrospective cohort study was reported at the 2016 Scientific Congress of the American Society for Reproductive Medicine.

Kevin S. Richter, PhD, of Shady Grove Fertility Reproductive Science Center, Rockville, Maryland, explained that he and colleagues set out to determine whether retrieval of larger cohorts of oocytes adversely affects outcomes of in vitro fertilisation.

All autologous in vitro fertilisation cycles among patients under 35 years of age from 2009–2014 were studied. Patients with diminished ovarian reserve, uterine factor, chromosomal abnormalities, or cancer; those being treated for fertility preservation, those using preimplantation genetic screening, oocyte or embryo cryopreservation prior to the blastocyst stage, or incomplete insemination of the retrieved cohort were excluded.

All embryo cryopreservation was performed using vitrification protocols at the expanded blastocyst stage (minimum inner cell mass grade B [several, loosely packed] and trophectoderm grade B [several cells organised in loose epithelium]) on day 5 or 6 after oocyte retrieval.

Potential births from the transfer of all vitrified blastocysts were estimated based on the observed birth rate of 35% per vitrified/warmed blastocyst among autologous patients.

A total of 8573 cycles were evaluated. Cycles with retrieval of one to four or five to nine oocytes were much less likely to display viable embryos available for transfer or cryopreservation, conferred much lower live birth rates per fresh embryo transfer cycle, and exhibited many fewer children per freshly transferred embryo vs larger retrieved oocyte cohorts.

The numbers of surplus blastocysts that were cryopreserved per fresh embryo transfer cycle, and the estimated total number of live born children resulting from the transfer of all fresh and cryopreserved embryos per oocyte retrieval cycle both increased substantially with each incremental increase in the size of the retrieved oocyte cohort.

Contrary to a 2011 study by Sunkara et al suggesting that a higher number of retrieved oocytes may yield a lower live birth rate, the present study of patients with a good prognosis shows that higher oocyte retrieval numbers do not adversely affect live birth per fresh transfer. In fact, more retrieved oocytes lead to higher numbers of vitrified embryos and ultimately higher live births per retrieval event.

"This research is clinically important because several groups have advocated milder ovarian stimulation in the belief that smaller cohorts of oocytes optimise in vitro fertilisation success rates," Dr Richter said.

"Our results refute this idea. We observed no decline in the percentage of freshly transferred embryos that went on to produce live born children in cycles with retrieval of more oocytes.

"We found no evidence to suggest that when more oocytes are retrieved, embryo quality or uterine receptivity to implantation and pregnancy are compromised. In addition, larger oocyte cohorts are associated with more high-quality surplus embryos that can be cryopreserved for later use.

"Our results indicate that retrieval of larger oocyte cohorts maximises the potential for live birth and the number of children per retrieval, and minimises the number of ovarian stimulation and oocyte retrieval procedures needed for patients to achieve their family-building goals."

Psychological burden drives insured patients to discontinue in vitro fertilisation

DENNY SAKKAS

When insured patients discontinue in vitro fertilisation treatment, the reason they cite is psychological burden.

Denny Sakkas, PhD, of Boston IVF, Waltham, Massachusetts, explained this outcome of the cross-sectional survey reporting, "We sought to find out why insured patients discontinue in vitro fertilisation treatment before they achieve a live birth." Their centre is a private academically affiliated in vitro fertilisation facility.

They sent a survey about treatment termination to 905 subjects whose final in vitro fertilisation cycle was between 2010 and 2014, who did not achieve a live birth, and who did not return to the centre for at least 1 year. The women completed the survey either online or by phone. Most Massachusetts residents are covered for six in vitro fertilisation cycles.

> "When asked what features might have improved their treatment experience, the most common responses ranged from opening hours to stress reduction strategies.

Thirty-six percent of 324 recipients (n = 324) completed the survey. Eighty-three percent of them (n=268) were fully or partially covered for in vitro fertilisation and were included in the analysis. Two thirds (66%) did not look for in vitro fertilisation at another centre but rather discontinued treatment altogether **(Figure 1)**.

The top three most reported sources of stress included:

- Having already given in vitro fertilisation their best chance (64%)
- Feeling too anxious or depressed to continue (51%)
- Infertility took too much of a toll on their relationship (39%).

Twenty-three percent of respondents said they conceived spontaneously. Of the remaining 34% who looked for care at another centre, the most common reason (60%) was that they sought a second opinion. When asked what features might have improved their treatment experience, the most common responses ranged from opening hours to stress reduction strategies (**Figure 2**).

Dr Sakkas concluded, "The most common reason insured patients reported discontinuing in vitro fertilisation treatment was psychological burden. They expressed a wish for stress reduction strategies. Providing such services may affect women's decisions to stop treatment before they achieve a live birth." ■

Figure 1. Reasons for discontinuing treatment

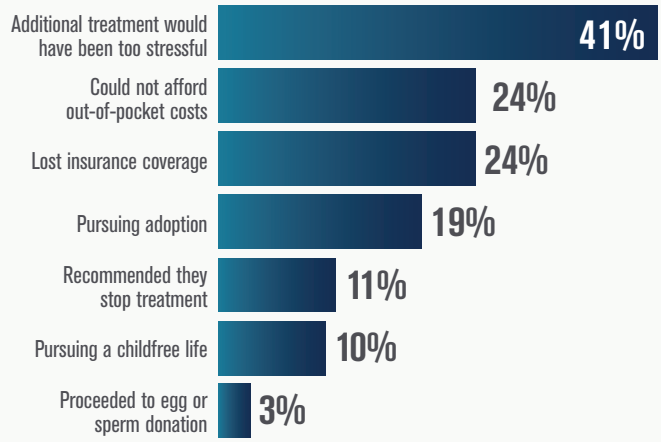
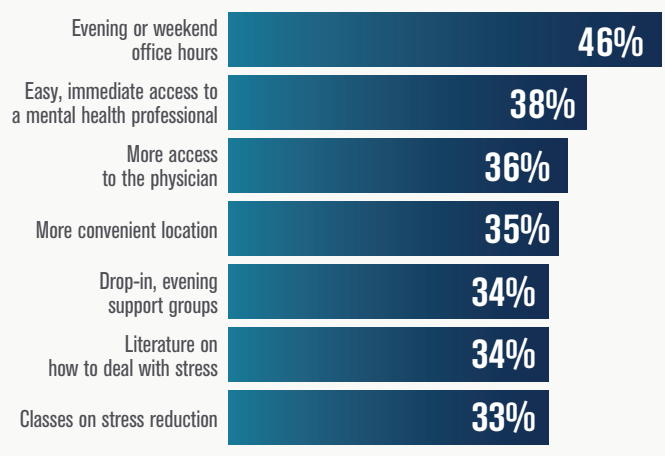


Figure 2. Features that would improve the treatment experience



Evaluation for endometrial polyps within 6 months of embryo transfer recommended

Within 6 months of an assisted reproduction procedure, saline infusion sonohysterography (SIS) should be performed or updated to identify and correct uterine abnormalities, according to a retrospective study presented by Kathryn Merriam, MD, of the University of North Carolina, Charlotte.

"We set out to find out how often SIS should be repeated in women preparing for embryo transfer."

The medical records of 194 women who underwent SIS prior to embryo transfer on two or more occasions from 2008–2013 were reviewed. Within 6 months before each embryo transfer, SIS was performed even if a prior SIS was normal.

The primary outcome studied was the incidence of an abnormal SIS during the first study. Secondary outcomes included:

- the incidence of an abnormal SIS in a subsequent study if initial SIS was normal
- the incidence of an abnormal SIS in a subsequent study if the initial SIS was abnormal.

Descriptive statistics were used in data evaluation.

The initial SIS was abnormal in 35 of 194 patients (18%), and 33 of the 35 women underwent corrective hysteroscopy. The most common uterine abnormality was endometrial polyps, confirmed in 60.6% of all hysteroscopies.

Eighty-two women underwent a second SIS. Of 64 with a normal initial SIS, 57 (89%) remained normal and seven (11%) became abnormal. Of 18 who had an abnormal initial SIS, 15 (83%) were normal and three (17%) were again abnormal during the second SIS. Approximately 20% of women were abnormal at both 6 and 12 months.

As expected, patients with an abnormal SIS exhibited significantly more days of menstrual bleeding than those with a normal SIS (mean 5.2 vs 4.7, P = 0.02). Peak endometrial thickness was significantly greater in patients with an abnormal SIS than in those with a normal SIS (P = 0.02). Even after correction (P = 0.04), the live birth rate was significantly higher in women with a normal SIS than in those with an abnormal SIS. The two groups did not differ significantly in any of the other variables.

Dr Merriam concluded, "The optimal time to repeat endometrial assessment in women undergoing assisted reproduction procedures has not been established, and the literature provides little guidance. Uterine abnormality incidence is high in infertile women undergoing assisted reproduction procedures".

Endometrial polyps may reduce endometrial receptivity, and hysteroscopic removal is recommended for infertile women undergoing in vitro fertilisation. The results support a policy of performing or updating the SIS within 6 months of an assisted reproduction procedure to help identify and correct uterine abnormalities before embryo transfer.

Genetic markers of egg cell quality may help diagnosis of women undergoing in vitro fertilisation

Subclinical, genetic markers of oocyte quality may help diagnose women undergoing in vitro fertilisation, independent of phenotypic biomarkers of fertility potential such as age and hormone levels.

This conclusion is based on results of a retrospective study of women who underwent in vitro fertilisation.

Piraye Yurttas Beim, PhD, of Celmatix Inc., New York, explained that when women with a good prognosis fail in vitro fertilisation for unexplained reasons, practitioners find that failure to be a challenge. Conversely, patients with a poor prognosis often achieve live birth.

Dr Yurttas Beim and coinvestigators sought to reveal subclinical, genetic factors that may help stratify patients before they decided to undergo in vitro fertilisation.

Between 2012 and 2015, 261 women underwent in vitro fertilisation at eight US fertility clinics.

"We used whole-genome sequencing," Dr Yurttas Beim said, "to identify genes that were predicted to be functionally disrupted across eight biological categories of relevance to infertility. These categories included oogenesis and the neuro-endocrine axis. We used discrete time proportional odds models to calculate the cumulative probability of ongoing pregnancy."

She continued, "Sequence kernel association testing, followed by burden testing, demonstrated that, after controlling for well-known predictive factors such as age and hormone levels, the presence of disruptions in genes related to oogenesis and poor egg quality resulted in a 50% decrease in the likelihood of ongoing pregnancy."

"When patients are failing in vitro fertilisation for unknown reasons, they are often told that poor egg quality may be blamed. This was the first study to back up that belief with real genetic data. This information could provide much needed clarity to unexplained infertility and help bring greater efficiency to infertility counselling and care."

In vitro fertilisation outcomes not affected by psychological stress

Pregnancy outcomes in women who undergo in vitro fertilisation are not affected by psychological distress.

Steven D. Spandorfer, MD, of Weill Cornell Medical College, New York presented this conclusion, based on results of a prospective, controlled trial, and explained, "We sought to assess the effects of psychological distress (depression, anxiety, and stress), assessed by both subjective and objective measures, on outcomes of in vitro fertilisation. We also described the pattern of psychological distress throughout the course of in vitro fertilisation".

Data collection time points during IVF

- the start of in vitro fertilisation
- oocyte retrieval
- embryo transfer
- the day of the pregnancy test

Women were divided into three groups:

- women who underwent in vitro fertilisation for the first time
- women who underwent in vitro fertilisation after having failed at least twice
- women who underwent in vitro fertilisation as oocyte donors.

Four questionnaires and serum levels of cortisol, adrenocorticotropic hormone, and interleukin-6 were used to measure stress. Pregnancy was documented by the presence of an intrauterine pregnancy on ultrasonography. One-way analyses of variance were applied for each of the four time points to compare mean stress levels related to anxiety, depression, and infertility. One hundred eighty-six patients underwent in vitro fertilisation between 2010 and 2013 for primary or secondary infertility.

Self-reported measures of depression, anxiety, and stress did not demonstrate an association with the outcome of in vitro fertilisation. The findings were further corroborated by the lack of an association between biological markers of stress and the outcome of in vitro fertilisation. The pattern of psychological distress, however, differed significantly among the three groups.

Higher levels of depression and stress were reported by both in vitro fertilisation treatment groups versus donors at the start of treatment and at retrieval. As determined by elevated cortisol level, donors experienced more direct, acute hypothalamic–pituitary–adrenal axis activation, however.

Cortisol levels dropped significantly at oocyte retrieval and embryo transfer, especially among donors, despite their rise in reported stress. Between embryo transfer and pregnancy, cortisol levels began to rise again a similar amount in both groups undergoing in vitro fertilisation. Those with repeated failures of in vitro fertilisation, however, reported the highest amount of psychological distress.

Dr Spandorfer concluded, "Psychological distress did not affect pregnancy outcome in women undergoing in vitro fertilisation. Reassuring patients that their stress level will probably not affect their chances of success of in vitro fertilisation is important, but sensitivity to the psychological distress of patients undergoing in vitro fertilisation is crucial, especially from embryo transfer to the pregnancy test."

Reaching out to patients who are more psychologically vulnerable due to prior failed treatment attempts may prove an important way to help reduce the burden of treatment and ultimately to lower patient dropout.

Breast cancer survivors on tamoxifen experience reduction in fertility

Women who take tamoxifen for breast cancer are less likely to give birth after cancer than women with breast cancer who do not take tamoxifen.

This conclusion is based on results of a population-based analysis presented by L. M. Shandley, MD, of Emory University, Atlanta, Georgia, who explained, "We sought to find out whether tamoxifen use is associated with decreased ovarian reserve and/or less probability of giving birth after their breast cancer diagnosis."

The Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's Study is an evaluation of reproductive-age women cancer survivors in Georgia.

> "Counselling tamoxifen users about pregnancy may help improve compliance with the drug and allow women to make more informed reproductive decisions.

The analysis included women 22–45 years of age who were diagnosed with breast cancer between the ages of 20 and 35 years and had been diagnosed at least 2 years prior to recruitment. After excluding those who underwent hysterectomy or bilateral oophorectomy before diagnosis, 397 survivors were analysed.

They were all interviewed about their reproductive history and their cancer treatments were abstracted from medical records. They had received at least 6 months of tamoxifen. Transvaginal ultrasonography and serum anti-Mullerian hormone levels were measured in 108 survivors.

Women who took tamoxifen were substantially less likely to give birth after their breast cancer diagnosis than those who did not take tamoxifen (hazard ratio 0.30, 95% CI 0.16–0.55). After adjusting for their age at diagnosis, alkylating agent exposure, and race, the hazard ratio was 0.18 (95% CI 0.09–0.38).

The association between tamoxifen and reduced likelihood of giving birth after cancer diagnosis was still strong among women who were childless at diagnosis (hazard ratio 0.36, 95% CI 0.17–0.77) and among women who had not met their reproductive goals at diagnosis (hazard ratio 0.33, 95% CI0.18–0.60).

Anti-Mullerian hormone and antral follicle count of women who did and did not take tamoxifen were compared with the goal of assessing the association between tamoxifen and ovarian reserve. Women who took tamoxifen exhibited estimated geometric mean anti-Mullerian hormone levels 2.47 (95% CI 1.08–5.65) times higher than those who did not take tamoxifen after adjusting for the following variables:

- age at clinic visit
- chemotherapy exposure
- cancer stage
- race
- gonadotropin-releasing hormone agonist use.

Tamoxifen users also demonstrated a higher antral follicle count (adjusted risk ratio 1.21, 95% CI 0.84–1.73).

Dr Shandley concluded, "Breast cancer survivors who took tamoxifen were less likely to give birth after a cancer diagnosis than breast cancer survivors who did not take tamoxifen. The ovaries of tamoxifen users were not found to have undergone additional damage beyond that of traditional breast cancer therapy".

The decreased likelihood of giving birth after a breast cancer diagnosis in women who took tamoxifen compared to those who did not take the drug may have been related to how long they took tamoxifen or concerns about pregnancy after taking tamoxifen. Counselling tamoxifen users about pregnancy may help improve compliance with the drug and allow women to make more informed reproductive decisions.

Ovulatory infertility coincides with lower breast density

Ovulatory infertility has been demonstrated to be associated with significantly lower percent mammographic density when compared with women whose partners exhibit male factor infertility.

LESLIE V. FARLAND

Leslie V. Farland, ScD, of Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts presented the results of this first study to investigate diagnoses of infertility, type of fertility treatment, and their association with mammographic density.

"High mammographic density is one of the strongest risk factors for breast cancer," she said.

Mammographic density is a measure of fibroglandular tissue. Women with high (>75%) mammographic density are at a four- to six-fold higher risk of breast cancer than those with low mammographic density.

> "When investigating associations with breast health, breast cancer, and other chronic diseases, understanding infertility mechanisms and their impact on hormonal and other milieu is important.

Mammographic density has been assessed in infertile women with mixed results. The association between mammographic density and infertility has not been evaluated however, by infertility diagnosis or type of fertility treatment.

Dr Farland and coinvestigators performed a cross-sectional analysis in 1281 premenopausal women who had not been diagnosed with breast cancer in the Nurses' Health Study II cohort.

A validated computer-assisted method was used to measure average percent mammographic density. Multivariable linear regression adjusted for age, current body mass index, body mass index at age 18, alcohol consumption, family history of breast cancer, smoking history, history of benign breast disease, parity, age at first birth, age at menarche, oral contraceptive history, and breastfeeding was used to estimate the association of ovulatory, tubal, cervical, and male-factor infertility diagnoses and fertility treatment (clomiphene and gonadotropin use), with percent mammographic density.

Infertility was defined as the unsuccessful attempt to conceive for >12 months. Among women who had experienced infertility, percent mammographic density 41.5% did not differ significantly from those who not experienced infertility. Women with ovulatory infertility had significantly lower average percent mammographic density (38.5%) than those whose infertility was attributed to male factor (mammographic density 43.2%, P = 0.02).

Women with tubal (mammographic density 36.1%) or cervical (mammographic density 44.1%) infertility did not differ in mammographic density from those with male factor infertility. Women who took only clomiphene (mammographic density 42.0%) or gonadotropin (mammographic density 44.1%) had similar mammographic density as those who did not take infertility medication.

"Women with ovulatory infertility harboured significantly lower percent mammographic density than women whose partners had male factor infertility," Dr Farland concluded. No association for infertility overall or for cervical or tubal infertility specifically was demonstrated.

"When investigating associations with breast health, breast cancer, and other chronic diseases, understanding infertility mechanisms and their impact on hormonal and other milieu is important," she added.

Low-dose levonorgestrel-releasing IUD highly effective over 5 years

The Skyla levonorgestrel-releasing intrauterine system has been found to be highly effective over 5 years.

KRISTINA GEMZELL-DANIELSSON

Kristina Gemzell-Danielsson, MD, of the Karolinska Institutet, Stockholm, Sweden, explained that she and colleagues set out in this randomised, open-label, phase 3 study to assess the 5-year efficacy and safety of Skyla levonorgestrel-releasing intrauterine system according to patients' age, parity, and body mass index.

"This was a development project to bring a new intrauterine system to market," said Dr Gemzell-Danielsson. "The goal of the International Committee for Contraceptive Research at the Population Council, of which I am a member, is to develop new safe and effective contraceptive methods to improve reproductive health.

"One of the most effective methods born within the committee is Mirena, a 52-mg levonorgestrel-releasing intrauterine system. Yet a smaller device with an even lower hormonal content was needed."

> "Intrauterine contraception is underutilised, and many young women suffer from anaemia and low iron levels. Intrauterine systems exert a positive impact by reducing bleeding and improving haemoglobin levels.

Women aged 18–35 years with regular menstrual cycles (21–35 days) who requested contraception were recruited. The full analysis set included 1452 women (mean age 27.1 years; 39.5% nulliparous; mean body mass index 25.3 kg/m^2). The 5-year Pearl Index score was 0.29.

Unadjusted 5-year Pearl Index scores were 0.18 (0.04–0.54) versus 0.36 (0.17–0.66) for women age 18–25 versus 26–35 years; 0.24 (0.07–0.63) versus 0.32 (0.15–0.61) for nulliparous versus parous women, and 0.24 (0.11–0.64) versus 0.56 (0.13–1.42) for women with body mass index <30 vs ≥30 kg/m^2.

The 5-year Kaplan-Meier cumulative failure rate was 1.4%. This rate was 1.2% versus 1.6% in nulliparous versus parous women, 0.9% vs 1.8% in women aged 18–25 versus 26–35 years, and 1.3% versus 2.2% in women with body mass index <30 vs ≥30 kg/m^2, respectively. Only 250 women had a body mass index ≥30 kg/m^2, so conclusions on contraceptive efficacy according to body mass index could not be drawn.

Risk of partial/complete expulsion was low regardless of patient age, parity, or body mass index. Cumulative 5-year expulsion rates were 3.7% for both age groups, 1.8% versus 5.0% for nulliparous vs parous women, and 3.1% versus 6.9% in women with body mass index <30 versus ≥30 kg/m^2.

The cumulative 5-year ectopic pregnancy rate was 0.18 per 100 woman-years (0.14–0.28 across all subgroups). Over 5 years, 328 (22.6%) women discontinued due to any adverse event. This rate was 24.2% versus 21.5% in nulliparous versus parous women. Overall, the most frequent adverse events that led to discontinuation were vaginal haemorrhage (3.5%), system expulsion (3.0%) and pelvic pain (3.0%).

Dr Gemzell-Danielsson concluded that the Skyla levonorgestrel-releasing intrauterine system was highly effective over 5 years, regardless of age or parity. The system was associated with low rates of expulsion and ectopic pregnancy. Overlapping 95% confidence intervals for all groups suggested no major differences between them. Skyla offers women a lower-dose 5-year contraceptive option.

Dr Gemzell-Danielsson said, "We have shown that a smaller intrauterine system results in less pain at placement. Pain at insertion is one of the major barriers to increased use of intrauterine contraception. Many women prefer non- or low-dose hormonal methods and local methods."

She added, "Intrauterine contraception with a levonorgestrel-releasing device is one of the most effective contraceptive methods available. It is safe, reduces bleeding, and confers several positive health benefits. This smaller, lower-dose device, combined several positive features, is easier to insert than larger devices, and is effective for the same 5-year duration. Intrauterine contraception, with the highest user satisfaction, is cost-effective and exerts low environmental impact."

"The World Health Organisation, International Federation of Gynecology and Obstetrics, and other agencies recognise that increased use of intrauterine contraception (belonging to the long-acting, reversible contraceptive class) will result in reduced maternal mortality and morbidity. This class, with its safety, high efficacy, and high user satisfaction, will reduce unplanned, unwanted pregnancy and unsafe abortions."

Finally, she said, "The goal of these agencies is to broaden the use of intrauterine systems in general, and specifically, to a younger age group. Intrauterine contraception is underutilised, and many young women suffer from anaemia and low iron levels. Intrauterine systems exert a positive impact by reducing bleeding and improving haemoglobin levels."

Woman's age when initiating hormone replacement therapy may affect her cognitive function

Age at initiation of hormone replacement therapy may modify associations between the therapy and both verbal reasoning and visual memory, according to a large prospective cohort study.

STAMATINA ILIODROMITI

"Hormone replacement therapy was associated with slightly worse visual memory in women who underwent menopause older than age 50 years, but the clinical significance of the difference in visual memory scoring is questionable.

Stamatina Iliodromiti, MD, PhD, of the University of Glasgow, UK, explains, "The role of hormone replacement therapy in cognitive function is disputed. We sought to find out whether the timing of hormone replacement initiation was associated with three different measures of cognitive function."

Data were derived from the UK Biobank, a prospective cohort of 273,467 women aged 40–70 years at recruitment (2006–2010). The database contains a wide range of phenotypic information.

Women who had experienced menopause at baseline were eligible for analysis. Cognitive function was evaluated using three computerised touchscreen tests to assess verbal–numerical reasoning, visual memory, and reaction time.

Regression models were adjusted for the following variables:

- age
- body mass index
- townsend deprivation index
- smoking
- history of cardiovascular disease or diagnosed diabetes.

Sensitivity analysis excluded patients who had undergone a hysterectomy and those with cardiovascular disease or diabetes.

A total of 162,818 patients were menopausal at recruitment, 85,252 of whom had never used hormone replacement therapy. Data on the age of initiation of hormone replacement therapy were available for 69,242 of 77,566 women who had used hormone replacement therapy.

Self-reported variables:

- use of hormone replacement therapy
- duration of treatment
- age commencing hormone replacement therapy
- age stopping hormone replacement therapy.

Hormone replacement therapy was associated with:

- lower verbal reasoning, –0.05 points (–0.1 to –0.001) for past users and –0.11 points (–0.17 to –0.04) for current users
- lower visual memory, –1.1% (0.2 to 2.0) for past users and 2.6% (1.1 to 4.2) for current users
- shorter (that is, better) reaction time, –0.6% (–0.8 to –0.3) for past users and –0.4% (–0.8 to –0.1) for current users.

Compared to women who had not taken hormone replacement therapy, verbal numerical reasoning was lower in those who commenced hormone replacement therapy at <40 years of age (–0.56 points [–0.69, –0.43]) and at 40–50 years of age (–0.13 points [–0.18, –0.09]), but did not differ substantially at age 50–60 or >60 years.

Timing of menopause, however, modified the above associations. Users who underwent menopause at age <40 years exhibited a 2.0% better reaction time (3.5 to 0.9).

Their visual memory was 5.0% better (10.0 to 0) than that of never users.

Hormone replacement therapy was not associated with verbal reasoning in these women.

Users who experienced menopause between 40 to 50 years of age demonstrated 0.5% better reaction time (1.0 to 0.1) than never users.

Hormone replacement therapy was not associated with verbal reasoning or visual memory in these women. In women who underwent menopause older than age 50 years, hormone replacement therapy was associated with an average of 2% poorer score on the visual memory test than never users.

Sensitivity analysis, excluding those who had undergone a hysterectomy and those with diagnosed cardiovascular disease and diabetes, did not modify the associations.

Dr Iliodromiti concluded, "Hormone replacement therapy is associated with better reaction time in women who underwent menopause under the age of 50 years, and better visual memory in those who underwent menopause younger than age 40 years."

She added, "Hormone replacement therapy was associated with slightly worse visual memory in women who underwent menopause older than age 50 years, but the clinical significance of the difference in visual memory scoring is questionable."

We are working to address unmet needs in reproductive health, focusing on the entire patient journey, from conception to birth.

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