

# Age-related fertility decline and elective oocyte cryopreservation

## *Knowledge, attitudes and practices in a pilot study of general practitioners*

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### Background and objective

Increasing numbers of women are experiencing age-related infertility. General practitioners (GPs) are ideally placed to provide initial age-related fertility counselling and fertility specialist referral. The aim of this pilot study was to document doctors' knowledge, attitudes and practices relating to proactive fertility counselling, ovarian reserve testing and oocyte cryopreservation.

### Methods

Seventy-two GPs and general practice registrars were recruited through social media and completed an online survey.

### Results

Knowledge gaps were shown relating to age-related female fertility decline, ovarian reserve testing and elective oocyte cryopreservation. GPs were more likely to discuss reproductive planning with women aged 35–44 years, compared with younger women. The majority of participants agreed fertility counselling should be provided by GPs; however, barriers identified include limited time, knowledge and concern for causing patient distress.

### Discussion

Providing GPs with fertility-focused education and resources may enable sensitive, accurate and timely counselling to improve reproductive outcomes.

**WOMEN AND COUPLES** are delaying having children until later ages when compared with previous generations.<sup>1</sup> The prevalence of female infertility increases with advancing age because of the biological limits of oocyte metabolism and function.<sup>2</sup> The risk of female infertility rises from 6% at age 20–24 years to 64% at age 40–44 years,<sup>3</sup> with the most significant reduction occurring from the ages of 37–38 years.<sup>4</sup> In this context, growing numbers of women and couples are being treated for age-related infertility.

Concurrently, a growing number of women are considering elective oocyte cryopreservation (EOC). EOC may allow conception of biologically related children later in life through in vitro fertilisation (IVF).<sup>5</sup> The reasons women consider EOC are complex. Commonly women feel unready to conceive in the immediate future, often associated with the absence of a partner's commitment to co-parenting.<sup>6,7</sup> EOC has been considered non-experimental since 2012.<sup>8</sup> It is used to store oocytes, ideally collected at a younger age when egg quality is better,<sup>4</sup> to be used later through IVF. With encouraging data emerging on safety and efficacy, the Australian and New Zealand Society for Reproductive Endocrinology and Infertility (ANZSREI) in 2019 described EOC as an ethically permissible, safe, well-established mainstream treatment.<sup>2</sup> The public are generally

aware of EOC and ovarian reserve testing and support it.<sup>9–12</sup>

Ovarian reserve testing, requisite to planning EOC,<sup>4</sup> includes measurement of anti-Müllerian hormone (AMH) and antral follicle count (AFC), which are helpful in assessing oocyte quantity and enable assisted reproductive technology (ART) practitioners to tailor treatment. Ovarian reserve testing does not predict fertility or fecundity outcomes.<sup>13</sup> Age remains the best predictor of IVF success, with live birth rates per blastocyst transfer of 40% in women aged <30 years, dropping to 11% in women aged 41–42 years.<sup>14</sup>

Patients' preferred first point of fertility education, investigation and referral for EOC are GPs.<sup>15</sup> The Royal Australian College of General Practitioners (RACGP) guidelines state that patients should be assisted in 'developing a reproductive life plan that includes whether they want to have children' and assisted in planning 'the number, spacing and timing of intended children'.<sup>16</sup> Patients expect GPs to be knowledgeable about fertility health and to be able to provide evidence-based information.<sup>15</sup> With increasing demand for EOC, it is important that GPs have accurate knowledge. It is not only patients who typically underestimate age-related fertility decline and overestimate success rates of ART,<sup>17–19</sup> but also medical professionals, including obstetricians and gynaecologists, family physicians

and nurses.<sup>20–22</sup> This raises concerns about whether women are receiving appropriate advice. The aim of this study was to explore GPs' knowledge, attitudes and practices relating to reproductive education, planning and EOC.

## Methods

Approval was granted by the Human Research Ethics Committee of the University of Melbourne (1853398).

GPs and general practice registrars were invited to participate in an online survey. No validated questionnaire on this topic has been published, so a novel questionnaire was constructed using Qualtrics. Recruitment was through Facebook groups Doc to Doc, Doctors in Training Victoria, Medical Mums and Mums to Be, the authors' personal pages, e-newsletters distributed via the RACGP and the Royal Women's Hospital, Melbourne (March to July 2019). To be eligible, participants had to be currently practising in Australia and provide consent.

The survey contained 41 questions developed to both assess and improve participants' knowledge of EOC, with the academic expertise of co-author RL, Reproductive Endocrinologist, Infertility Subspecialist and author of ANZSREI Consensus Guideline on EOC<sup>2</sup> and MP, Program Leader for Psychosocial Health and Wellbeing Research (emPoWeR) Unit, Department of Obstetrics and Gynaecology, University of Melbourne.

Facilitated learning was a recruitment incentive. After participants' baseline knowledge was assessed, correct responses, supporting information and references were provided. Where participants selected 'other', free text boxes were provided for further comment. Questions and responses are shown in Tables 1–5.

## Analyses

Incomplete surveys were excluded from analysis. Data were analysed with SPSS version 24 and Microsoft Excel. Postcodes were assessed for rurality using the Accessibility/Remoteness Index of Australia.<sup>23</sup> Total knowledge scores were calculated as the sum of correct responses

(1 = correct, 0 = incorrect). Themes from free-text responses were explored. Associations between reservations about referring on for EOC (dichotomised: yes vs no or unsure) and likelihood of asking about reproductive plans or elective fertility preservation (dichotomised: likely vs neither or unlikely), attitude towards family planning counselling (dichotomised: agree vs neither or disagree), and frequency of ordering AMH (dichotomised: > annually vs < annually) were explored using Chi-squared tests. A student's t-test was used to compare mean knowledge scores between those who had reservations about EOC and those who did not or were unsure. Free-text responses were analysed for common themes.

## Results

### Demographics

Seventy-two GPs and general practice registrars participated. Although a large variety of participants were represented, the majority were younger female GPs in metropolitan areas (Table 1). The average time to complete the questionnaire was 16 minutes (standard deviation [SD] = 7).

### Knowledge

While 82% of participants were aware that EOC is no longer considered experimental, 40% were incorrect on timing of female fertility decline (Table 2). The average knowledge score was 5.4/12 (SD = 1.8; range = 0–9). Participants showed poor understanding of ovarian reserve testing. Forty per cent failed to identify that AMH was not a measure of oocyte quality/natural fertility. Quantitative interpretation of AMH levels was also poorly understood.

### Counselling, attitudes and practices

Participants reported infrequent discussion of elective fertility preservation with patients (Table 3). Sixty-seven per cent were asked about EOC by patients semi-annually or less, and 92% referred patients for EOC semi-annually or less.

Eleven per cent reported reservations regarding EOC. Having reservations was associated with reduced likelihood to

**Table 1. Demographic characteristics of participants**

Characteristic	n (%)
<b>Profession</b>	
General practitioner	57 (79.2)
General practice registrar	15 (20.8)
<b>Age (years)</b>	
25–34	33 (45.8)
35–44	21 (29.2)
45–54	11 (15.3)
55–64	6 (8.3)
65–74	1 (1.4)
<b>Sex</b>	
Male	5 (6.9)
Female	66 (91.7)
Unspecified	1 (1.4)
<b>Location</b>	
Major city	40 (55.6)
Regional	24 (33.3)
Remote	5 (6.9)
Unmatched/unspecified	3 (4.2)
<b>Special interest</b>	
Women's health or similar	21 (29.2)
Other	11 (15.3)
None	40 (55.6)
<b>How did participants hear about this survey?</b>	
Social media	46 (63.9)
Flyer	1 (1.4)
Colleague	4 (5.6)
Email	8 (11.1)
Friend	2 (2.8)
RACGP e-newsletter	13 (18.1)
Other	2 (2.8)

RACGP, The Royal Australian College of General Practitioners

**Table 2. Knowledge on fertility and fertility preservation and ovarian reserve testing (n = 72); the correct answer is marked with an asterisk**

Question	n (%)
<b>The largest reduction in natural fertility occurs during which age range?</b>	
20–29 years	4 (5.6)
30–34 years	6 (8.3)
35–37 years*	43 (59.7)
38–40 years	19 (26.4)
<b>Oocyte cryopreservation is no longer considered experimental according to the ASRM and the ESHRE.</b>	
True*	59 (81.9%)
False	1 (1.4)
Unsure	12 (16.7)
<b>Oocyte cryopreservation is now considered very effective.</b>	
True*	43 (59.7)
False	14 (19.4)
Unsure	15 (20.8)
<b>While individual circumstances must be considered, which comment regarding the age at freezing is incorrect?</b>	
Many women have cryopreserved oocytes over the age of 35 years.	11 (15.3)
The highest live birth rate is seen when oocytes are cryopreserved at younger ages.	9 (12.5)
Age-related decline in fertility is primarily related to the decline in the quality of the oocyte as it ages and not the age of the uterus.	8 (11.1)
The age of the women at time of freezing is not a good predictor of oocyte potential.*	44 (61.1)
<b>Which is not a risk of oocyte cryopreservation?</b>	
Ovarian hyperstimulation syndrome	2 (2.8)
Risks during oocyte collection including infection, damage to organs, blood loss, ovarian torsion, risks related to anaesthesia	1 (1.4)
Increased risk of congenital abnormalities*	60 (83.3)
Financial risk (eg cost of medication, cycles, IVF, etc)	1 (1.4)
Long-term risk associated with IVF	3 (4.2)
Risks of child bearing at advanced maternal ages	1 (1.4)
Unspecified	1 (1.4)
<b>Who can provide assisted reproductive technologies?</b>	
Gynaecologists	2 (2.8)
Gynaecologist with expertise in fertility	15 (20.8)
Fertility specialist	18 (25.0)
Gynaecologist with reproductive endocrinology and infertility training (CREI)	21 (29.2)
All of the above*	49 (68.1)

ASRM, American Society for Reproductive Medicine; CREI, Certificate of Reproductive Endocrinology and Infertility; ESHRE, European Society for Human Reproduction and Embryology; IVF, in vitro fertilisation

ask about reproductive plans ( $\chi^2 = 3.87$ ,  $P = 0.049$ ) or discuss EOC ( $\chi^2 = 4.35$ ,  $P = 0.037$ ) with patients aged 18–34 years, but not with the 35–44-year age group ( $\chi^2 = 3.48$ ,  $P = 0.062$ ;  $\chi^2 = 0.08$ ,  $P = 0.783$ ; respectively). A similar association was seen between reservations and attitudes towards elective fertility preservation counselling with the 18–34-year age group ( $\chi^2 = 6.05$ ,  $P = 0.014$ ) but not the 35–44-year age group ( $\chi^2 = 1.53$ ,  $P = 0.217$ ). Reservations were not associated with knowledge score ( $\bar{X}_{\text{yes}} = 5.5(1.9)$  vs  $\bar{X}_{\text{no/unsure}} = 5.4(1.8)$ ,  $t(60) = -0.148$ ,  $P = 0.883$ ). Common reservations related to concerns regarding efficacy (38%), costs (25%) and lack of knowledge (13%). One respondent commented:

*[I] feel that a social shift in the workplace regarding women having children younger is required, rather than put the onus on women to take on financial and medical risks of oocyte storage, plus risk of future infertility.*

Participants were less likely to ask women aged 18–34 years about their reproductive plans when compared with women aged 35–44 years. Barriers cited were time constraints (61%) and wishing to avoid causing stress (33%):

*Concerns about perpetuating social pressures for women to procreate, when that may not be their wish/desire/goal.*

Seventy-eight per cent felt fertility decline counselling should occur with women aged 18–34 years, and 94% agreed it should be discussed at 35–44 years. Most (83%) felt GPs should be the health professional to do this.

Fifty-three per cent reported being ‘very unlikely’ or ‘neutral’ about initiating an elective fertility preservation discussion in patients aged 18–34 years, with 30% retaining this attitude for ages 35–44 years. The most common barriers to counselling were lack of time (57%) and insufficient knowledge (25%) and resources (15%).

The majority (96%) believed women were delaying having children as a result of not having the right partner, career aspirations (93%) and ‘not wanting



**Table 3. Counselling and practices regarding reproductive planning and fertility preservation (n = 72) (Cont'd)**

Question	n (%)		Question	n (%)	
<b>How likely are you to initiate a conversation regarding elective fertility preservation with a patient/couple that is desiring future pregnancy and delaying because of non-medical reasons for patients aged ...</b>	<b>18-34 years</b>	<b>35-44 years</b>	<b>What are the main barriers to oocyte cryopreservation in women/couples delaying pregnancy for non-medical reasons? (All that apply)</b>		
Very unlikely	10 (13.9)	6 (8.3)	Knowledge	61 (84.7)	
Somewhat unlikely	12 (16.7)	7 (9.7)	Financial	67 (93.1)	
Neither likely or unlikely	16 (22.2)	8 (11.1)	Efficacy	19 (26.4)	
Somewhat likely	22 (30.6)	21 (29.2)	Ethical reservations	17 (23.6)	
Very likely	12 (16.7)	30 (41.7)	Religious beliefs	13 (18.1)	
<b>What are the main barriers to initiating this conversation?</b>			Physical risks/side effects	24 (33.3)	
Time constraints	41 (56.9)		Time commitment	41 (56.9)	
Insufficient resources	11 (15.3)		Other (Mostly rural/remote access. Also partner involvement, fear)	7 (9.7)	
Reservations about fertility preservation	8 (11.1)		<b>Please indicate to what extent you agree/disagree that women are sufficiently aware of age-related reduction of fertility in:</b>	<b>themselves</b>	<b>men</b>
Insufficient knowledge	18 (25.0)		Strongly agree	6 (8.3)	0 (0.0)
Discomfort	5 (6.9)		Somewhat agree	37 (51.4)	8 (11.1)
Not my responsibility	2 (2.8)		Neither agree nor disagree	3 (4.2)	10 (13.9)
To avoid causing stress for patient	16 (22.2)		Somewhat disagree	22 (30.6)	37 (51.4)
<b>What do you think are the main reasons that some women/couples may wish to delay having children? (All that apply)</b>			Strongly disagree	4 (5.6)	17 (23.6)
Career	69 (95.8)		<b>Please indicate to what extent you agree/disagree that men are sufficiently aware of age-related reduction of fertility in:</b>	<b>themselves</b>	<b>women</b>
Education	57 (79.2)		Strongly agree	0 (0.0)	9 (12.5)
Travel	57 (79.2)		Somewhat agree	7 (9.7)	36 (50.0)
Not ready	61 (84.7)		Neither agree nor disagree	4 (5.6)	6 (8.3)
Have not found the right partner yet	71 (98.6)		Somewhat disagree	36 (50.0)	14 (19.4)
Saving money	61 (84.7)		Strongly disagree	25 (34.7)	7 (9.7)
Do not want children currently but concerned about changing mind in future	62 (86.1)				
Other (Patient's current health issues)	3 (4.2)				

children currently but concerned about changing mind in the future' (84%). The main perceived barriers were lack of knowledge of EOC (82%) and cost (90%).

A majority 'somewhat' or 'strongly' agreed that men (63%) and women (60%) were sufficiently aware of female age-related infertility, but that men (85%) and women (75%) were not sufficiently aware of men's fertility reducing with age.

Ovarian reserve testing was not commonly requested (Table 5), with 75% requesting it semi-annually or less. On receiving a high AMH result, 19% offered reassurance regarding current fertility to patients <35 years and 11% for patients aged ≥35 years. With a very low AMH result, the majority of participants would arrange immediate fertility specialist referral (64% for patients aged <35 years;

78% for patients aged >35 years). The requirement for nuanced counselling on the AMH test was reflected on (for low AMH):

*Advise lower than average ovarian reserve but explain complexity of the test and reassure based on age, offer fertility specialist referral if wished (but this is why I avoid ordering AMH).*

**Table 4. Attitudes and practices regarding ovarian reserve testing (n = 72)**

Question	n (%)	
<b>How often do you request ovarian reserve testing, in total, for all patients?</b>		
Weekly or more	0 (0)	
Monthly	4 (5.6)	
Quarterly	14 (19.4)	
Semi-annually	14 (19.4)	
Annually or less	40 (55.6)	
<b>In the last year, how often have you ordered an AMH test?</b>		
Weekly or more	0 (0)	
Monthly	5 (6.9)	
Quarterly	14 (18.1)	
Semi-annually	7 (9.7)	
Annually or less	47 (65.3)	
<b>As an estimator of ovarian reserve, in which scenarios do you order an AMH test?</b>	<b>Younger than 35 years</b>	<b>Aged 35 years and over</b>
Pre-pregnancy investigation	1 (1.4)	14 (19.4)
Unable to conceive after trying for >6 months	17 (23.6)	36 (50.0)
Infertility investigations	35 (48.6)	39 (54.2)
Investigation prior to referral to fertility specialist	40 (55.6)	45 (62.5)
Post chemotherapy or ovarian surgery	15 (20.8)	14 (19.4)
On patient request	30 (41.7)	32 (44.4)
Other: (Most common answer was 'never', only in infertility context, and when requested by patient and after discussion about relevance)	12 (16.7)	11 (15.3)
<b>What is your next management step after receiving a very low AMH result? Tick all that apply.</b>	<b>Younger than 35 years</b>	<b>Aged 35 years and over</b>
Advise low chance of conceiving	5 (6.9)	6 (8.3)
Immediate referral to fertility specialist	46 (63.9)	56 (77.8)
Arrange other fertility investigations	32 (44.4)	30 (41.7)
Management unchanged	6 (8.3)	3 (4.2)
Other: (Most common answers were 'never order' or 'ask the patient')	11 (15.3)	10 (13.9)
<b>What is your next management step after a high AMH result? Tick all that apply.</b>	<b>Younger than 35 years</b>	<b>Aged 35 years and over</b>
Offer reassurance regarding current fertility	14 (19.4)	8 (11.1)
Immediate referral to fertility specialist	8 (11.1)	22 (30.6)
Arrange other fertility investigations	24 (33.3)	26 (36.1)
Management unchanged	18 (25.0)	18 (25.0)
Other: (Frequent answers were 'consider PCOS', 'never', counsel in context of fertility)	21 (29.2)	16 (22.2)

AMH, anti-Müllerian hormone; PCOS, polycystic ovary syndrome



**Desire for training and resources**

Most participants (92%) agreed that more information should be made available on EOC, preferably online (78%), with one participant suggesting an:

*Article or module produced in co-operation with [the] RACGP.*

**Discussion**

This is the first Australian study to assess GP knowledge, attitudes and practices regarding reproductive ageing and EOC.

Participants' general knowledge of fertility was good; however, gaps were identified, including some estimating the age of onset of biological fertility decline too late, at 38–40 years, when it occurs at 35–37 years.<sup>14</sup> Many participants did not

identify age as the foremost predictor of successful EOC, with best efficacy shown when eggs are frozen before the age of 36 years.<sup>4</sup> Knowledge of ovarian reserve markers, their interpretation and clinical utility was lower than general fertility knowledge. GPs surveyed overestimated their patients' awareness of women's fertility reducing with age, with the majority of GPs agreeing that men and women are sufficiently aware of women's fertility reducing with age; however, studies have shown that patients, as well as obstetricians and gynaecologists, underestimate the reduction of fertility with age.<sup>18–20</sup> This is concerning when GPs are expected to discuss reproductive planning,<sup>16</sup> with 83% of participants feeling this was their role. Yet, only 12% of women undergoing EOC first learnt

of it from a doctor, with more learning of it via peers or the media, and women wished they had undergone EOC at a younger age, stating lack of awareness as the reason for not doing so.<sup>24</sup> Earlier discussion facilitates earlier, more effective EOC treatment.<sup>2</sup> However, participants with reservations about EOC were less likely to discuss EOC with their younger patients. It may take women many years to decide to freeze oocytes (Sandhu S, Hickey M, Braat S, Lew R, Peate M, unpublished), and given the ultimate importance of timing for optimal efficacy, women need to be aware of EOC from a relatively early age.

Common barriers to family planning discussions were lack of time, knowledge, resources and fear of 'causing stress' for the patient. GPs may feel uncomfortable raising the topic of fertility with patients, concerned about perpetuating gendered stereotypes and applying perceived societal reproductive pressure. Prior et al reported younger Australian men and women would not feel uncomfortable if their GP brought up this topic (91% and 87%, respectively).<sup>25</sup> It is, however, important, that information given is reliable. In light of the low knowledge level of ovarian reserve testing, most GPs were referring as appropriate to fertility specialists for counselling in context of a low AMH result. However, some participants offered patients with a normal or high AMH result false reassurance about current and future fertility. With women increasingly interested in EOC, there is an urgent need to support GPs to provide an accurate interpretation of AMH to avoid increasing distress or providing false reassurance. Providing further education for GPs and funding for provision of counselling would help to facilitate accurate and timely discussions.

Study participants infrequently referred patients for EOC, with cost a barrier. EOC attracts no government rebate and costs approximately \$6885–\$8000 per cycle (more than one may be needed) in addition to annual storage fees and future costs associated with IVF,<sup>26</sup> a personal cost that is perceived to be high by those who have undergone EOC.<sup>27</sup> However, allowing concern regarding the cost to

**Table 5. Further training and resources wanted by participants**

Question	n (%)
<b>More information on elective oocyte cryopreservation should be made easily available to general practitioners</b>	
Strongly agree	40 (55.6)
Somewhat agree	26 (36.1)
Neither agree nor disagree	6 (8.3)
Somewhat disagree	0 (0.0)
Strongly disagree	0 (0.0)
<b>Additional information should be on: (All that apply)</b>	
Live birth outcomes for different providers	54 (75.0)
Available training	23 (31.9)
Procedures and logistics	44 (61.1)
Costs and cost benefit considerations	67 (93.1)
Other fertility preservation options	49 (68.1)
Ovarian reserve testing/pre-referral investigations	62 (86.1)
Other: (no suggestion provided)	1 (1.4)
<b>Additional information should be in the format of: (All that apply)</b>	
Brochure	33 (45.8)
Website	56 (77.8)
Video	7 (9.7)
Training in person	23 (31.9)
Training online	39 (54.2)
Other: ('article' and no suggestion provided)	2 (2.8)

direct whether the conversation occurs does not consider patient autonomy and informed choice. To make an informed decision about use of elective ART, patients should be informed of all appropriate options. Informed choice can guide decisions that are consistent with personal values, which may include a willingness to self-fund EOC.

The limitations of this study include selection bias, limited sample size and lack of a validated questionnaire. Additional reservations and concerns may be held by non-participant GPs. Older GPs and male GPs have not been well represented, which may be a reflection of lack of interest in this field and/or limitations in the recruitment method. Sample size limited generalisability and the ability to explore associations. However, in the absence of any research in this area, this study can provide some insights – noting in particular that participants are likely to be those with an interest in reproductive health and thus these data may show higher knowledge and rates of discussion, more positive attitudes and greater rates of referral than GPs at a population level. Future research could look to validate the survey and collect data on a larger, more representative sample.

### Implications for general practice

Participants in this pilot study displayed some gaps in knowledge of fertility, ovarian reserve testing and EOC. These include that reproductive planning discussions including EOC could be entered into at earlier life stages to offer women greater biological insight, perspective and choice. Participants requested more online fertility-focused education and training. The findings suggest a place for additional resources to assist GPs in providing timely and accurate counselling to enable patients to achieve their reproductive life plans.

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