Ovarian reserve screening: a scientific and ethical analysis

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Submitted on June 19, 2014; resubmitted on August 15, 2014; accepted on September 19, 2014

ABSTRACT: Ovarian reserve (OR) screening of the general population is generally not advocated as it has not been conclusively established to reflect immediate potential for natural conception, while it may also potentially create anxiety for women. However, in this paper, we argue in support of screening of the general population for diminished OR. First, OR tests such as measurements of anti-Müllerian hormone and antral follicle count are predictive of the chances of IVF conception, and therefore predict a woman’s total fertility potential (i.e. chances of natural and IVF-related conceptions). Since the requirement for assisted conception increases with age, this is an important point. Secondly, women identified as having low OR are at increased risk of early loss of fertility potential in the longer term, limiting their reproductive life span and the size of their family if they delay conception. Thirdly, women often disregard generic advice to avoid delaying conception beyond 30 years of age, yet studies suggest that personalized risk assessment tools such as OR testing can actually increase an individual’s motivation for positive change. A poor OR screening test result is more likely to convince a woman to bring forward her plans for natural conception, or alternatively explore oocyte vitrification, at a stage when these approaches still have reasonable prospects of success. Finally, we believe that women have a right, based on the ethical concept of autonomy, to be made aware of OR screening, so that they themselves can determine if OR testing is useful in assisting them with reproductive life planning.

Key words: ovarian reserve / AMH / AFC / screening / ethics

Introduction

Ovarian reserve (OR) is determined by the net result of the initial size of the primordial follicle endowment, the natural rate of atretic loss and the impact of any insult to the ovary that may hasten follicle depletion. Given these multiple determinants, it is not surprising that there is significant biological variability in OR between individuals of the same age and hence variation in the age of onset of subfertility and the menopause (Te Velde and Pearson, 2002; Goswami and Conway, 2005).

Studies of fertility in societies that do not practice contraception, for example, the Hutterite Brethren, suggest that 11% of women have no further children beyond 35 years of age, and that on average, there is a 10-year gap between the age of mothers at the birth of their last child and the onset of menopause (Tietze, 1957; Te Velde and Pearson, 2002). Therefore, since 10% of the general population is known to be menopausal by 45 years of age, one would expect up to 1 in 10 women to become involuntary sterile by their mid-30s due to a critical loss of OR.

Prior to the 1970s, premature loss of OR was not a major concern since most women tended to start their families early, with premature loss of OR only likely to marginally constrain the ultimate size of their family, rather than cause childlessness (Joffe et al., 2009). However, with the advent of effective contraception, plus an increase in women’s participation in higher education and the workforce (Mills et al., 2011; Ni Bhrolchain and Beaujouan, 2012), there has been a significant increase in the average age of first time mothers across the developed world [OECD, 2012; Schmidt et al., 2012; Martin et al., 2013; Office National Statistics (UK), 2013]. This trend is even more marked for tertiary educated women, with approximately one in five now delaying their first pregnancy until after 35 years of age (Schmidt et al., 2012). Not surprisingly, this has resulted in a doubling in the incidence of involuntary childlessness in the last two decades (Te Velde et al., 2012).

Professional societies such as the ASRM and ESHRE have mounted education programmes to better inform both men and women of the risks to their fertility from delaying parenthood (Soules and American Society for Reproductive Medicine, 2003). However, despite significant media coverage, these campaigns have not resulted in any significant changes in actual reproductive behaviour since the average age of first time mothers has not declined (Martin et al., 2013). While both men and women are now more aware of diminishing fertility with age, they still significantly overestimate female fertility potential beyond 35 years of age (Lampic et al., 2006; Bretherick et al., 2010; Bavan et al., 2011; Hashiloni-Dolev et al., 2011; Peterson et al., 2012). Clearly, new approaches are required.
The underlying reasons why public education campaigns have failed to change reproductive planning behaviour are likely to be complex, but we would suggest two key factors. First, both men and women significantly overestimate the ability of IVF to successfully treat diminished OR (advanced maternal age)-related infertility. This is not surprising given the media’s obsession with publicizing cases of celebrity women having babies with the aid of IVF in their mid-40s, with no reference to the use of donor oocytes. This creates an erroneous perception that medical advances in IVF can help women have their own biological child late in reproductive life. Secondly, experience suggests that ‘generic’ educational campaigns often have limited effectiveness if the target population believe that the advice does not apply to them. For example, surveys have reported that many women believe that regular exercise, a healthy diet or even a fertile family history, all protect them from age-related fertility decline (Ryan et al., 2005; Bavan et al., 2011; Hashiloni-Dolev et al., 2011; Mac Dougall et al., 2013). Since diminished OR is generally a silent disease, these ‘healthy’ women will have a false sense of security, possibly resulting in poor decisions to delay starting a family.

OR screening may hold some promise in giving an individual woman a better idea of her personal OR status, rather than just providing her with generic age-related fertility advice. Surveys suggest that three-quarters of women of reproductive age are interested in knowing their own OR status, with 80% of participants in one survey stating that they would bring forward their plans for children if faced with an adverse OR screening result (Bavan et al., 2011; Aguinaldo, 2014). Serum anti-Müllerian hormone (AMH) concentrations and ultrasound-determined antral follicle count (AFC) are the best tests of OR as they have been reported to be excellent markers of quantitative OR when analysed against both historically assessed primordial follicle numbers (Hansen et al., 2011), or quantitative response to gonadotrophin stimulation in IVF treatment (reviewed in La Marca et al., 2010; Broer et al., 2013).

Previous commentaries have suggested that OR screening of the general population is unwise for a number of reasons (Loh and Maheshwari, 2011). First, at the present moment, there is only limited evidence suggesting that OR screening actually reflects immediate natural fertility potential. Secondly, an adverse OR result may create anxiety, especially among single women who cannot readily bring forward their plans for starting a family. Finally, some would argue that health expenditure would be better made on other more worthy initiatives. However, in our opinion, these views are scientifically flawed and ethically misguided. Therefore, the purpose of this paper is to discuss the scientific merit behind OR screening, before moving on to discuss the ethical imperative to offer OR screening to all young women who seek its assistance to help them better plan their reproductive life.

**Argument for OR screening**

**The link between quantitative and qualitative OR and natural conception**

The decline in female fertility with advancing age is related to a reduction in both the number and quality of oocytes, with the increase in oocyte aneuploidy mirroring the decline in residual OR (ACOG, 2014; Fransasiak et al., 2014). While AFC and AMH are generally considered more as measures of quantitative OR, rather than a direct marker of oocyte quality (Smeenk et al., 2007; Lie Fong et al., 2008; Loh and Maheshwari, 2011; Broer et al., 2014), animal studies do suggest that quantitative and qualitative OR are inter-related since unilateral oophorectomy has been reported to result in an immediate increase in the rate of oocyte aneuploidy (Brook et al., 1984; Eichenlaub-Ritter et al., 1988). Similarly, several studies have reported an increased chance of conceiving a genetically abnormal pregnancy or having a miscarriage for women with diminished OR (Freeman et al., 2000; van Montfrans et al., 2001; Sahu et al., 2010; Grande et al., 2014). Furthermore, one prospective study has reported a significant reduction in the chances of immediate conception (in the next 6 months) in those women with diminished OR (AMH ≤ 0.7 ng/ml), even after controlling for the confounder of maternal age (Steiner et al., 2011). However, other contradictory studies have reported no increase in the rate of embryo aneuploidy in women with low OR (Lie Fong et al., 2008), nor any increase in the risk of miscarriage (Tremellen and Kolo, 2010), and a prospective Danish study did not observe a reduction in the chances of immediate natural conception in the presence of diminished OR (Hagen et al., 2012). However, this latter study’s conclusion was weakened by its use of a relatively high AMH cut-off value for defining poor OR (AMH < 1.96 ng/ml or 14 pmol/l), and a low statistical power due to the very low number of patients who had a critical loss of OR.

**Redefining the ‘goal posts’ for a useful test of fertility potential**

Because of the lack of consensus surrounding the ability of OR screening to predict immediate natural conception potential, many reproductive physicians suggest that it is unwise to advocate screening of the general, non-infertile population. We would like to counter argue that this approach is flawed for three main reasons.

**The primary outcome should be chances of IVF as well as natural conception**

Opponents of OR screening appear only concerned with its ability to predict immediate natural conception. While all women will have a preference for natural rather than IVF conception, it is our belief that their primary concern is not whether they will conceive naturally, but rather whether they will become parents. As such, any consideration of the value of OR screening to predict fertility potential must consider both natural and IVF-related conception which we have termed ‘total fertility potential’. While we acknowledge that IVF-related births make up only a small proportion of the total number of births in a population (Sundram et al., 2013), we believe that as the risk of requiring IVF to conceive increases with maternal age (Kocourkova et al., 2014), it is misleading for an OR screening test to prognosticate only for natural conception, disregarding IVF conception.

It is well established that both AMH and AFC are excellent predictors of a woman’s response to gonadotrophin stimulation during IVF treatment. A woman with a low AMH (<0.5–0.8 ng/ml) or low AFC (<5–7) has an 80–90% chance of responding poorly to IVF stimulation, producing three or fewer oocytes (Ferraretti et al., 2011; Broer et al., 2013). With such low oocyte numbers, the chances of producing a good quality blastocyst for transfer are relatively slim, thereby significantly reducing the chances of pregnancy (La Marca et al., 2010; Holte et al., 2011). A large cohort study of over 400 000 cycles of IVF reported that pregnancy rates increased with up to a yield of 15 oocytes, but women producing only 4 oocytes had a half of the pregnancy rate of...
those with an 'optimal response' (15 oocytes), and women producing only 2 oocytes had a quarter of the pregnancy rate of the optimal response group (Sunkara et al., 2011). While some investigators have suggested that OR markers such as AMH are not predictive of pregnancy in IVF (Broer et al., 2013), or have limited predictive value (Iliodromiti et al., 2014), these meta-analyses, in our opinion, are flawed by analysing data from studies with excessively high AMH cut-off points, and limiting their analysis to fresh embryo transfer cycles. Our group (Lekamge et al., 2007) and others (Nelson et al., 2007; Arce et al., 2013) have shown that when cumulative pregnancy rates, consisting of pregnancies resulting from the transfer of all embryos from one stimulated cycle of IVF (both fresh and subsequently frozen embryo transfers), are considered, AMH and AFC have a very significant predictive value for pregnancy. Since the main cost of IVF, both in terms of finances and patient discomfort, is the stimulated IVF cycle, this cumulative pregnancy assessment is the more clinically meaningful result, which means that the focus should not just be on fresh embryo transfer outcomes.

The time frame of reference should be long term

Opponents of OR screening suggest that because the current evidence does not conclusively show that low OR significantly reduces a woman’s chances of pregnancy in the immediate term (next 6 months), the test must have no clinical value. However, this is short-sighted, since several studies have shown that a low age normalized AMH result will result in that woman going through an earlier menopause, and therefore an earlier onset of sterility (van Rooij et al., 2004; Broer et al., 2011; Tehrani et al., 2013). For example, a 28-year-old woman with an AMH result of only 0.5 ng/ml will on average become menopausal by 40 years of age (Tehrani et al., 2013). If she were to try for pregnancy immediately, she is likely to have a positive outcome. However, as the onset of sterility predates menopause by an average of 10 years (te Velde and Pearson, 2002), she is likely to be at a significant risk of secondary infertility by her early to mid-30s. Therefore, this abnormal OR test result has significant implications for this woman with regard to the potential final size of her family (Leridon and Slama, 2008).

OR screening personalizes the risk

Human nature often results in a tendency for people to think that adverse life events will not happen to them; this is an adaptive emotional shield. Daniel Kahneman writes in his book ‘Thinking Fast and Slow’ of a ‘pervasive optimistic bias’, which generates the illusion that we have substantial control over our life events. This optimistic life perception extends to reproduction since several studies have reported that both men and women still consistently overestimate female reproductive capacity beyond 40 years of age. Therefore, we suggest that without recourse to OR screening to better inform women of their actual likely reproductive life span, many women will not be making effective reproductive life plans.

Although controversial, research in other fields of medicine supports the principle that personalised risk assessment by utilizing medical technology such as genetic testing is more effective in changing people’s behaviour than generic advice (Frosch et al., 2005; Smerecnik et al., 2007; Meisel et al., 2012; Schneider and Schmidtke, 2014). For example, studies have reported improvements in the rate of successfully quitting smoking if an individual’s own personalized risk of lung cancer is found to be elevated compared with other smokers using genetic risk profiling (reviewed in Schneider and Schmidtke, 2014). In this example, every smoker is already aware that smoking causes lung cancer, but despite this knowledge they have still smoked, since in their own mind, this increased risk was not material for them. However, once they have a test result which informs them of a significantly increased risk of cancer than the average smoker, that risk becomes personalized and more effective in changing their behaviour. Similarly, while public awareness campaigns have resulted in the majority of women knowing that fertility declines with time; many disregard this advice as irrelevant to their own situation because they erroneously believe that their own healthy lifestyle or good family history of fertility is protective in some way. In our view, a poor OR screening test result is more likely to personalize the risk of diminished OR for that individual, leading to better informed reproductive planning decisions.

Does OR testing meet the WHO criteria for an adequate screening test?

The WHO have developed 10 criteria for assessing the adequacy of a screening test (Wilson and Jungner, 1968). We believe that serum AMH testing of OR currently meets all but one WHO screening criteria (Number 7). Tables I and II summarize the points for and against OR screening.

(i) Criteria 1. The condition sought should be an important health problem for the individual and community. The potential end result of early diminished OR, involuntary childlessness or

<table>
<thead>
<tr>
<th>Table 1 Points in favour of OR screening.</th>
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<tr>
<td>1. Loss of ovarian reserve is a significant problem, resulting in sterility in up to 10% of women by their mid-30s</td>
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<td>2. Loss of ovarian reserve is often clinically silent until the point where there is little hope for pregnancy. Therefore, early identification using ovarian reserve screening is critical</td>
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<td>3. AMH and AFC are excellent markers of quantitative OR, but possibly do not reflect oocyte quality and therefore chances of immediate natural conception. However, a poor AMH or AFC result does reflect a marked reduction in the chances of IVF-related conception</td>
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<td>4. The best yard stick for judging the value of an ovarian reserve screening test is its ability to predict total fertility potential (natural plus IVF-related conception), since women are primarily concerned with their ability to become parents, not the mode of conception. AMH and AFC do predict total fertility potential</td>
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<td>5. A poor ovarian reserve test result signifies an increased risk of early menopause and decline in fertility, possibly limiting a woman’s ability to complete the family of her desired size</td>
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<td>6. The majority of women are interested in learning of their own ovarian reserve status, with up to 80% indicating they would bring forward plans for pregnancy if faced with a poor result</td>
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<td>7. Educational programmes warning women of the dangers of delaying conception have limited impact. Ovarian reserve screening personalizes the risk, potentially improving motivation for better reproductive life planning</td>
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<td>8. Once identified as having premature loss of OR, a woman may bring forward plans for natural conception, or may opt for oocyte vitrification or immediate donor sperm treatment if single</td>
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<td>9. Physicians have an ethical duty to inform women of the availability of ovarian reserve screening, and its relative merits and plans for action. Autonomy dictates that patients should be the ones who decide whether they proceed with ovarian reserve screening</td>
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secondary infertility is of major importance to a woman and her partner’s health. Involuntary childlessness has been linked with increased rates of depression, poor self-esteem, social isolation and even suicide in women (Wirtberg et al., 2007; Schwedtfejer and Shreffler, 2009; Kjaer et al., 2011).

(ii) **Criteria 2.** There should be an accepted treatment or useful intervention for patients with the disease. Provided diminished OR is identified early enough (<35 years of age), evidence suggests that women still have a good chance of successfully conceiving if they commence trying immediately. If conception has not occurred within 6 months, consideration should be given to early investigation and treatment as studies suggest that the vast majority (88%) of natural conceptions should have occurred within this period (Gnoth et al., 2003). Furthermore, this recommendation is consistent with ACOG/ASRM guidelines (Committee Opinion No. 589, 2014) suggesting expedited evaluation and treatment of infertility for women older than 35 years of age, which is the group also exhibiting diminished OR.

Alternatively, women with diminished OR may elect to cryopreserve their oocytes, allowing them to preserve some fertility potential until later in life if they are not in a position to start a family immediately (Goold and Savulescu, 2009). Finally, women may elect to become single mothers by undertaking donor sperm fertility treatment if their OR results are poor and they perceive their chances of finding an appropriate partner in the near future as being remote.

(iii) **Criteria 3.** The natural history of the disease should be adequately understood. It is well established that quantitative OR declines with advancing age, and that this decline, together with a reduction in the quality of the oocytes, is responsible for the age-related decline in fertility. It is also well established that large variances in OR status exist between individuals, resulting in different fertility potentials at the same chronological age.

(iv) **Criteria 4.** There should be a latent or early symptomatic phase. OR testing is capable of detecting compromised OR well before patients become symptomatic (with menstrual shortening or irregularity) or have reached a point where they have absolutely no fertility potential. OR screening has no role in the woman older than 35 years as all women have compromised oocyte quality by this stage and none should be encouraged to delay pregnancy, irrespective of the OR screening result.

(v) **Criteria 5.** There should be a suitable and acceptable screening test or examination. Serum AMH is an excellent non-invasive marker of OR. While there have been problems with the accuracy of some AMH ELISA assays, these technical issues have now been resolved (Han et al., 2014), and two new automated AMH assay platforms provide high precision results, at increased speed and reduced costs. AFC requires a transvaginal ultrasound for optimal accuracy, reducing its acceptability to some women. While AFC assessments must be conducted in the early follicular phase of a woman’s menstrual cycle, serum AMH can be taken at any time since it fluctuates very little within the cycle (La Marca et al., 2010) or between menstrual cycles over the short term (Hehenkamp et al., 2006); thereby making AMH the ideal primary tool for OR screening. Those women found to have a low initial AMH result should have a follow-up early follicular phase AFC assessment, plus a repeat serum AMH and FSH to confirm the diagnosis of diminished OR.

The oral contraceptive (OC) can suppress AMH and AFC results for up to 2 months after discontinuation of the hormones (van den Berg et al., 2010), and therefore, it is ideal to screen OR when off the OC. Alternatively, women can be screened while on the OC, but those with low results should have a confirmatory repeat test after 2 months off the OC.

(vi) **Criteria 6.** Facilities for diagnosis and treatment should be available. Women may undergo IVF treatment which will not only confirm or refute the diagnosis of diminished OR (determined by oocyte response to maximal dose gonadotrophin stimulation), but may also provide oocytes for use in cryopreservation or fertility treatment.

(vii) **Criteria 7.** There should be an agreed policy on whom to treat as patients. Neither AMH nor AFC-based OR testing currently meets this WHO screening criterion (Loh and Maheshwari, 2011; Nelson et al., 2012), as there are no large prospective observational studies that can be used to guide the development of cut-off values for AMH and AFC that conclusively indicate when OR is diminished to the point that it represents a threat to immediate or medium term fertility (i.e. a period of time sufficient to complete a family, not just have one child). Until these studies are completed, we would suggest that an AMH result below the 10th percentile for age, confirmed on repeat testing, and backed up by a low AFC result, is a reasonable point to suggest that fertility potential is likely to be compromised. The use of the 10th percentile cut-off is consistent with the ~10% incidence of sterility by the mid-30s in non-contracepting populations (Tietze, 1957), and the expected incidence of OR-related sterility linked with early menopause (te Velde and Pearson, 2002). However, we acknowledge that this policy requires more research and the development of a consensus view by societies such as ESHRE and ASRM.

(viii) **Criteria 8.** Treatment started at an earlier stage should be more of benefit than treatment started later. Since OR and natural fertility decline with age in all women, any poor OR screening test result that influences a woman to bring forward her plans to start a

### Table II Points against OR screening.

| 1. | Studies to date have not conclusively proven that a poor ovarian reserve screening result has any implications for immediate (next 6 months) conception potential |
| 2. | Ovarian reserve screening may create unnecessary anxiety for women, leading to premature truncation of their education or career progression |
| 3. | Ovarian reserve screening costs money which could be better used on other health priorities. Simple education to convince women not to delay fertility is a less expensive approach |
| 4. | Ovarian reserve screening may increase the number of women undergoing oocyte vitrification and related ART treatments, increasing costs to the individual and community |
| 5. | A poor ovarian reserve screening test may cause a single woman to make plans to become a single mother, with possible concerns for the child (no father figure, less financial security than a dual parent family) |
| 6. | A good ovarian reserve screening result may suggest to a patient that it is safe for her to delay conception until much later in life (≥35 years), when fertility is diminished irrespective of ovarian reserve status |
| 7. | A doctor has an ethical duty not to create unnecessary anxiety, especially if a screening test is not 100% accurate |
family is of course more likely to result in a positive pregnancy outcome. As previously outlined, identifying women with diminished OR by screening (to provide a personalized risk assessment) is more likely to motivate women to bring forward their plans for conception, rather than just generic advice not to delay conception.

Criteria 9. The cost should be economically balanced in relation to possible expenditure on medical care as a whole. It is anticipated that OR screening costs would be borne by the individual, not the public purse, and therefore would not significantly reduce resources for other competing medical needs. However, some forms of diminished OR-related treatment are likely to be subsidized by the government or by health insurance. While we consider this entirely appropriate as diminished OR is a medically recognized cause of infertility, we will elaborate on this topic further in our later discussions on distributive justice.

Criteria 10. Case finding should be a continuing process and not a once-and-for-all project. We suggest that OR screening should be offered to all women ~30 years of age, or possibly at an earlier age if they have a particular risk factor for early loss of OR. Screening before the mid-20s is unlikely to be cost-effective due to a low prevalence of critical loss of OR, plus young women are less likely to be in an established relationship or prepared to immediately bring forward their plans for children if faced with a poor result. A later onset of OR screening, such as at 30 years of age, has the advantage of decreasing the size of the population requiring screening, since many women will have completed their family by age 30, plus the majority of women are in established relationships by this age and therefore able to act on a poor result. Finally, OR screening should not be initiated beyond 35 years of age as fertility is already impaired in all women by this age, irrespective of their OR screen result.

Table III summarizes what we believe to be an ideal protocol for OR screening and subsequent management of diminished OR, based on the discussions above.

### An ethical assessment of OR screening

OR screening poses ethical challenges for many clinicians and their patients. In today’s world of ‘evidence based medicine’, many clinicians look solely to science to answer questions about the usefulness of tests such as OR screening, yet science can only provide information with varying degrees of confidence and probabilities. How we deal with that information concerning probabilities provided by OR testing, however uncertain or incomplete, is an ethical, not just a scientific, question (Savulescu and Hope, 2010). Furthermore, ethics is even more important when dealing with interventions that are not strictly about treating or preventing disease, but rather have social or personal value to patients.

A common framework used in medical ethics is the ‘four principles’ approach that recognizes four basic moral concerns (autonomy, beneficence, non-maleficence and justice), which are judged and weighed against each other in order to help make a final deliberation (Gillon, 1994). We will discuss each of these ethical principles in relation to how they apply to OR screening.

### Autonomy

Autonomy means literally self-rule or self-determination. Autonomy relates to an individual’s freedom to weigh up the pros and cons of OR screening for herself, in the context of their own desires of what constitutes a desirable and fulfilled life. Different women will place different emphasis on the importance of being able to become mothers, or when to have children or having their own biological child. Some woman may never want children and for this group, OR screening is unnecessary. Others may be accepting of the small risk that they will run out of oocytes and will need to resort to donor oocyte IVF to have a child, but the vast majority of women consider that becoming a mother of their own biological child is a key life goal (Bretherick et al., 2010; Peterson et al., 2012). Furthermore, the relative merits of OR screening sensitivity and specificity will also vary among women. For example, a woman who perceives motherhood as an essential goal may be quite accepting of an OR screening test that has a relatively high false-positive rate, provided that it identifies declining fertility at an early stage when chances of pregnancy are still excellent (high sensitivity, low specificity). Conversely, a career-focused woman may be more concerned about the potential for a false-positive test result that may lead to unnecessary anxiety concerning the need to start a family in the near future, interrupting her career progression. For this woman, the OR test would have to have high specificity to be useful to her. For these reasons, it is important to educate women about the sensitivity and specificity of OR testing, in the context of their own life goals.

### Table III - Proposed protocol for OR screening

| 1. Ovarian reserve screening should be offered to all women at 30 years of age who potentially seek future fertility. Screening must be voluntary. Screening may be offered earlier if significant risk factors are present |
| 2. Pre-screening counselling regarding the decline in fertility with age and the merits and potential actions related to ovarian reserve screening must be performed before the test is ordered |
| 3. AMH is the ideal screening test of ovarian reserve as it is the least expensive and intrusive, has the least inter-observer variability and can be taken at any stage in the menstrual cycle |
| 4. A serum AMH result below the 10th percentile for age suggests that the individual has diminished ovarian reserve. A repeat confirmatory AMH and FSH test (Days 3–5, off hormonal contraception for 2 months) should be performed, together with an AFC scan. A final risk assessment is made after consideration of all results, in the context of any known individual risk factors for diminished ovarian reserve |
| 5. Abnormal results must be discussed with a reproductive medicine physician with an understanding of the relative merits of the test and the available treatment options |
| 6. Women seeking pregnancy after a poor ovarian reserve screen result should be encouraged to attempt natural conception for 6 months, unless natural conception is impossible or highly improbable (e.g. in the case of tubal factor infertility, severe semen defect or no partner). If conception does not occur within 6 months, early recourse to treatment should be considered |
| 7. Patients with borderline low ovarian reserve screening results may elect to have follow-up ovarian reserve testing 12 months later to assess the rate of decline in ovarian reserve before acting on the result |
Medical paternalism is the undesirable practice where doctors make their own judgements of what is best for their patients, without involvement of the patient herself. Such paternalism is out dated and fails to respect patients as people. Doctors should by all means form views of what they judge to be best for their patients, and make recommendations to them, but should also engage them in dialogue and ultimately respect their own judgements for what is best for them, within the constraints of distributive justice (Savulescu, 1995, 1997). The decision to be tested or not, and actions that follow from those screening test results, is a decision to be made by the informed patient, not unilaterally by the medical profession. We certainly do not advocate universal screening of OR as this too may infringe women’s autonomy and their wishes to remain ignorant.

Of course, patients have a right to the best quality information available. We should continue to vigorously research OR testing. Every person using this technology should be encouraged to enter a prospective survey that tracks pregnancies in relation to OR screen results. Ongoing audit and research will no doubt provide better quality evidence that can be conveyed to patients. However, patients have a right to access the fruits of science, even at an early stage, provided they are aware of the risks as far as they are known (Halpin et al., in press).

Critics may suggest that it is inappropriate for a medical professional to expect a non-medically educated patient to make an informed decision regarding OR screening, when the doctor is in the best position to assess its potential merits. However, as the relative merits of OR screening are dependent on the person’s life goals and circumstances, the patient and not the doctor, is in the best position to balance the relative merits of screening. Furthermore, the social group most likely to take up OR screening is the professional class who have delayed starting their family to advance their education and career. This group is likely to have good skills in critical reasoning and therefore are more than capable of making informed decisions regarding whether to have OR testing, and ultimately what actions they take as a result of screening.

Finally, there is a persuasive argument that if the medical profession are willing to prescribe contraceptives which allow women to delay having children, then it is inconsistent for them to deny access to OR screening. Without testing, how is a woman to know if delaying conception is reproductively safe for her? The loss of OR is a silent condition; especially when the sentinel symptoms of diminished OR (shortening of menstrual cycle or irregularity) are hidden by the use of the OC pill. Failing to offer OR testing in this context is not allowing the woman access to the entire relevant facts from which she can make her own life course decisions; in our view, this is a breach of patient autonomy.

Beneficence and non-maleficence

The guiding principle of medicine is that doctors will always strive to do good for their patients (beneficence), while avoiding harm (non-maleficence). However, there is no medical intervention of benefit, including screening tests, which is totally devoid of risks. Therefore, the doctor and patient must assess the balance of risks and benefits, supporting those interventions that show a net benefit. From the previous discussions, we believe that we have mounted a persuasive argument about the potential benefits of OR screening (Table I). However, to assess net benefit, we must also consider the potential negatives, as summarized in Table II.

Opponents of OR testing suggest that a good result may encourage women to delay pregnancy beyond their early 30s, when chances of success are diminished even in the presence of good OR. However, we reject this view since it is not a weakness of OR screening but rather poor patient education. We do not advocate OR screening beyond 35 years of age, since it is never advisable to delay pregnancy beyond this age. However, OR screening may be useful in providing younger women reassurance that delaying starting a family for a year or two is unlikely to result in diminished OR-related sterility.

One of the more legitimate concerns regarding OR screening arises when considering testing a woman who is not in a supportive, established relationship. Here, a poor OR result creates a reproductive dilemma as these women cannot readily start trying for natural conception. They may elect to freeze their oocytes, a process that now offers a reasonable chance of success (Dondorp et al., 2012). However, gonadotrophin stimulation with oocyte retrieval is not without risk (of surgical complications or OHSS), although those risks do appear to be relatively small in women with low OR (Bodri et al., 2008).

Some women with diminished OR will elect to become single mothers by undergoing donor sperm ART, raising concerns about conceiving a child with no prospect of a relationship with their biological father. However, research suggests that the psychological outcomes for these children are generally good and certainly no worse than that of the general population (Murray and Golombok, 2005; Weissenberg and Landau, 2012). Appropriate surrogate father figures may be found (future husband, maternal grandfather, uncle), and surely the prospective mother is in a better position to assess her capability to parent (both emotionally and financially) than her treating physician.

Distributive justice

Distributive justice in the medical context is the moral obligation to act fairly in the allocation of limited medical resources between competing medical needs. In OR screening, the medical resource costs lie with the provision of the screening test (e.g. serum AMH), and possibly with follow-up fertility treatment (oocyte vitrification, donor sperm ART). Now that several automated platforms for AMH assessment are coming to the market, it is likely that the cost of AMH-based OR screening will become relatively inexpensive. AFC-based OR screening cannot be automated, and for this reason is likely to be more expensive than serum AMH-based screening.

From a distributive justice perspective, we acknowledge that the use of public funds to pay for treatment such as oocyte cryopreservation for single women would of course mean that less money is available to spend on other worthwhile health-care priorities. We accept that it would be wrong to divert funding from activities such as cancer prevention to OR screening and treatment, as prevention of cancer is a higher priority. However, we believe that such discussions are disingenuous when it is women themselves who are responsible for their own OR screening costs, together with the bulk of any related ART services. Public funding is not normally made available for ‘social oocyte freezing’, even if backed by a legitimate medical need such as poor OR. Therefore, offering OR testing is unlikely to significantly limit the availability of scarce medical resources for other more worthwhile clinical needs.

Equality requires that patients in similar situations should have access to the same health-care opportunities. As diminished OR is a cause of subfertility, why should women experiencing this as a cause for their infertility not receive appropriate medical funding support? We do not make moral judgements barring women with blocked fallopian tubes
resulting from past STD’s from accessing IVF treatment. Therefore, why should we deny women access to appropriate screening and treatment of diminished OR-related infertility, just because they have made a conscious decision to advance their education and career? Equality would dictate that they have a right to access screening technology and possibly ART treatment if clinically appropriate.

Overview

It should now be evident to the reader that screening for OR is a complex medical and social question. While we acknowledge that AMH and AFC are imperfect tests of natural fertility potential, this paper has highlighted four previously unreported reasons why these tests should at least be considered for adoption as part of an OR screening campaign. First, AMH and AFC are valid tests of total fertility potential (natural plus IVF-related conception). Women may be more concerned with becoming parents than with the mode of conception and therefore physicians should cease dismissing OR screening just because it may not reflect immediate natural fertility potential. Secondly, a poor OR screen test suggests an earlier onset of menopause and decline in fertility, potentially limiting the size of a woman’s family. Making women aware of this allows them to begin a family earlier and/or to shorten the time interval between children, maximizing their chances of achieving their optimal size family. Thirdly, surveys have reported that women do welcome the opportunity to be informed of their own OR status, and are often prepared to change their life priorities when faced with a poor OR result. Personalized risk assessment, such as that provided by OR screening, is more likely to result in a change in a woman’s reproductive life plans than just generic advice. Finally, we believe that autonomy demands that physicians inform their patients of the availability of OR testing, together with its relative merits and associated treatments, so that women can make their own decision on whether or not to be tested.

Acknowledgements

We would like to thank Bill Ledger and Sheryl de Lacey for their critical review of the draft manuscript.

Authors’ roles

K.T. was responsible for the concept, drafting and final approval of the manuscript. J.S. was responsible for development of the ethical analysis, revision and final approval of the manuscript.

Funding

Neither the authors nor the institution received payment or services from a third party for any aspect of the submitted work.

Conflict of interest

K.T. is a minor shareholder in the IVF service provider Monash IVF which also conducts ovarian reserve screening. K.T. has previously been engaged in commercially sponsored research relating to AMH assay development (Elecsys® AMH platform, Roche) for which he received no personal remuneration. J.S. has no conflicts of interest to declare.

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