Australian Evidence-based Guideline for Unexplained Infertility: ADAPTE process from the ESHRE Evidence-based Guideline on Unexplained Infertility 2023

Public consultation

Public consultation dates: Friday 20 October until Sunday 19 November 2023

Stakeholders invited to submit:

- Consumer health forum
- Director-General, Chief Executive or Secretary of state, territory and Commonwealth departments of health
  - Department of Health Victoria
  - Department of Health South Australia
  - Department of Health WA
  - Department of Health Qld
  - Department of Health NSW
  - Department of Health TAS
  - Department of Health ACT
  - NT Heath.
  - Australian Government Department of Health and Aged Care.
- Fertility Society of Australia and New Zealand (FSANZ)
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
- Royal Australian College of General Practitioners (RACGP)
- Guideline development group members
- CRE WHiRL Chief and Associate Investigators
- Australian Indigenous Doctors Association
- European Society for Human Reproduction and Embryology (ESHRE)
- Victorian Assisted Reproductive Technology Assoc
- Publicly promoted via NHMRC Tracker, NHMRC's fortnightly newsletter.

Stakeholder comments from public consultation

ID	Comment/ GDG response
1	Incomplete submission. No response required.
2	**Guideline recommendation to which feedback is targeted.** It is recommended that at least 12 months of unprotected sexual intercourse before initiating fertility interventions. In Australia, it is recognised that clinical investigation may commence earlier in the case of a couple who are older or may want more than one child. Whilst frequency of intercourse should not affect the definition of infertility, in couples seeking to conceive, it could be reasonable to advise to increase sexual intercourse to at least every 2-3 days within the fertility window to the extent that such suits their own preference. **Comment** The report misstates the ICMART definition. The guidelines should be clear that they apply only to heterosexual couples. While that may sound obvious, given the topic, there may be some clinicians who are reluctant to accept that a same sex couple or a single intended parent is infertile until 12 months has passed, for the purposes of Medicare and clinically relevant service. Adding "heterosexual" to the second paragraph under narrative question, line two, so that it reads "infertility, heterosexual couples", instead of "infertility, couples" will fix the issue. **GDG response/ action** Add "heterosexual" first line page 6 Introduction. "About 30% of heterosexual couples…." Covered very thoroughly under terminology on page 8 so little change needed
3	Incomplete submission. No response required.
4	Incomplete submission. No response required.
5	Incomplete submission. No response required.
6	**Comment** [redacted] is the peak national body for community and professional education in male reproductive health. Our expertise was not sought during the development of the document and we learned of this process via the FSANZ secretariat. This is regrettable given [redacted] has a long-established relationship with the Australian fertility community and FSANZ through postgraduate education and data collection, as well as within the Monash Department of O&G. That said, given the works stems from the well-considered

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	guidelines of ESHRE, we agree with the recommendations overall. We are certainly happy the need for male clinical history and examination have been included. We make one observation. Definition: "Mild factor male infertility" has not been defined. As pointed out there is a variety of definitions in the literature. They suggest that any abnormalities on routine semen testing equate to ˜male factor" and thus not "UI" as stated; "The GDG proposes that results from a basic semen examination below the lower 5th percentile reference limit (and its 95% confidence interval) should be considered as clinically relevant for decision making about further clinical investigation. However, anything outside this reference excludes unexplained infertility" (p.27). Such a strict interpretation overlooks the fact that the predictive value of each sperm parameter is limited aside from azoospermia, complete immotility or gross types of teratospermia. One does not want to reinforce the misperception in patients and doctors that semen analysis is a direct test of sperm function or fertility; it is only descriptive, with cut-offs taken at the 5th centile of men of known fertility. The problem is that finding inconsistent or borderline values in one or more WHO parameters is exceedingly common. In one report fewer than 15% of Australian males have semen analysis results that consistently meet all WHO criteria for "normal" (see 'justification and evidence' section). The majority of these males will not have fertility problems. Thus, a large proportion of couples will fall outside the definition of "unexplained infertility" (as the semen analysis would "explain" the problem) and may be directed toward ART. The pathways described for UI may be appropriate in selected cases. One might soften the wording and acknowledge that many fertile men may have one or two parameters just outside the 5th centile [e.g. a progressive motility of 27%], and even on repeat sampling. Accordingly, one should not preclude the clinician making a balanced decision to apply the UI approach to these couples. **Justification** WHO semen reference criteria (Cooper et al., 2010) were all met by only 52 (14.4%) men. In the remainder, some criteria were not met in the first semen analysis for semen volume (<1.5 ml, 14.8%), total sperm number (<39 million, 18.9%), sperm concentration (<15 million/ml, 17.5%), progressive motility (A + B grade motility <32%, 14.4%) and morphologically normal sperm (<4%, 26.4%), while all five WHO criteria were not met for four participants (1.1%). See https://doi.org/10.1093/humrep/dev244 **GDG response/ action** We acknowledge the comments but the guideline development group for ESHRE, the extensive international consultation and the Australian GDG are all aligned with the diagnosis of unexplained infertility requiring a normal semen analysis. Add Practice Point It is recognised, based on semen samples from Australian men of unproven fertility, that many may not fulfil all aspects of the WHO criteria (with a reference)
7	**Comment** Thank you for inviting the [redacted] to make a submission to the Centre for Research Excellence in Women's Health in Reproductive Life (CREWHiRL) on Australian Evidence-based Guideline for Unexplained Infertility: ADAPTE process from the ESHRE Evidence-based Guideline on Unexplained Infertility 2023.consultation. [redacted] is the lead standards body in women's health in Australia and New Zealand, with responsibility for postgraduate education, accreditation, recertification, and the continuing professional development of practitioners in women's health, including both specialist obstetricians and gynaecologists, and GP obstetricians. [redacted] supports the development and content outlined in the guideline and recognises its significance in providing valuable guidance in infertility practices. Whilst the summary is useful[redacted] emphasises the importance of delving into the full guidelines for a comprehensive understanding of the recommendations. This approach allows practitioners to grasp the nuanced justifications behind each statement, enabling a more informed perspective. [redacted] acknowledges that the guideline is based on current evidence. However, the field of infertility presents a unique challenge as there is a shortage of evidence for many aspects of this practice. Recognising these gaps in evidence facilitates a nuanced and tailored approach to patient care, particularly in situations where evidence is limited or absent. This approach ensures that infertility treatments address the needs of individual patients, resulting in a more patient-centred and evidence-informed approach. To this end, [redacted] supports the development of the Australian Evidence-based Guideline for Unexplained Infertility: ADAPTE process from the ESHRE Evidence-based Guideline on Unexplained Infertility 2023 and looks forward to seeing the effects of its implementation. [redacted] acknowledges with thanks, the contribution of [redacted] for this submission. **GDG response/ action** Nil needed
8	**Comment** I would like to congratulate with the Australian GDG and Steering committee for the excellent work done. My special thanks go to the colleagues who have directly built the recommendations and to those who have contributed to the Australian adaptation. I am sure that this step will further strengthen the support for healthcare professionals and, ultimately, for couples affected by UI.

ID	Comment/ GDG response
	Few comments from my side: 1. I see that the Australian GDG decided not to provide an age threshold for the definition of UI, even though considering female age as an issue. In the adaptation, it is also suggested to go for clinical investigation earlier than 12 months in couples who are "older" (it is not indicated after how many months of attempts). My feeling is that this could lead to premature, unnecessary, medicalization of the couple and may exacerbate the subjectivity in management. **GDG response/ action** The Australian GDG has made the following practice point: " Female age is a consideration in UI, with male age a less significant factor, at more extreme age", which acknowledges the importance of advanced maternal age in unexplained infertility. The Australian GDG was reluctant to nominate a specific age cut off, i.e. age 40, as the effect of maternal age is a continuous one and not binary at a specific age. This was not an evidence-based recommendation or practice point in the ESHRE guideline and no evidence was sought to determine any specific age cut off in the ESHRE guideline. 2. The Australian GDG decided not to adopt FIGO definition of normal menstrual cycles, but to define them as cycles with length < 35 days, based on a large study and on PCOS GL. Even if I agree on the risk of ovulatory dysfunctions in women with a cycle length at the upper limit of the normal range, I still think that consistency among the most important scientific societies should be pursued worldwide. **GDG response/ action** We agree consistency is important. FIGO dealt with menstrual dysfunction. The PCOS guideline and Unexplained Infertility guideline deal with infertility, are consistent and evidence based. We acknowledge that we differ to FIGO and ESHRE in this respect and that there is still some controversy in the area 3. Mild male factor is excluded from the diagnosis of UI. The justification is not clear enough regarding what "mild" means. **GDG response/ action** This guideline addresses unexplained infertility and hence, defining mild male factor is not within the scope of this guideline (see also above comment). 4. I much appreciate the research recommendation on hysteroscopy for the detection and possible correction of intrauterine abnormalities not seen at routine imaging. **GDG response/ action** No change required 5. Most of the recommendations on male additional tests and genetic screening were downgraded in strength in Australia due to low certainty of evidence. I deem it as a wise choice, independently of the integrity check. The same applies to some recommendations on treatment (e.g. antioxidant). **GDG response/ action** No change required
9	Incomplete submission. No response required.