

## Full application for an addition of a test categories in the EDL

### Survey response 1

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#### 1. Name of test category

|                                                                 |
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| Name of the test category addressed in the original submission: |
| Serum Follicle-Stimulating Hormone (FSH) Test                   |

#### 2. Pre-submission information

|                                                                      |
|----------------------------------------------------------------------|
| Please indicate your pre-submission response ID: [Pre-submission ID] |
| 291                                                                  |

#### 3. Applicant's information (primary contact person):

|                                                                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------|
| Contact person, name and information of the person submitting the application: [LAST NAME, First name]                               |
| KABRA, Rita                                                                                                                          |
| Contact person, name and information of the person submitting the application: [Email address (...@....)]                            |
| kabrar@who.int                                                                                                                       |
| Contact person, name and information of the person submitting the application: [Phone number (+country code) phone number no spaces] |
| +41 22 791 1092                                                                                                                      |
| Contact person, name and information of the person submitting the application: [Other information]                                   |
| Technical Officer                                                                                                                    |

#### 4. Applicant's information (secondary contact person):

|                            |
|----------------------------|
| [LAST NAME, First name]    |
|                            |
| [Email address (...@....)] |
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|                                                       |
|-------------------------------------------------------|
| [Phone number (+country code) phone number no spaces] |
|                                                       |
| [Other information]                                   |
|                                                       |

## 5. Details of the organization making the submission (if applicable)

|                                                                                            |
|--------------------------------------------------------------------------------------------|
| Name of the organization making the submission (if applicable): [Name of the organisation] |
| WHO                                                                                        |
| Name of the organization making the submission (if applicable): [Address]                  |
|                                                                                            |
| Name of the organization making the submission (if applicable): [Department]               |
|                                                                                            |
| Name of the organization making the submission (if applicable): [Website]                  |
|                                                                                            |
| Name of the organization making the submission (if applicable): [Phone number]             |
|                                                                                            |

## 6. Details of the organizations supporting the application:

|                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------|
| Please provide up to three organizations supporting your application including a. Organization name, b. Contact person, c. Email address: |
|                                                                                                                                           |

## 7. Public health impact of the disease/condition:

Please detail the public health relevance of conditions addressed with the proposed test and add references:

FSH is a polypeptide hormone produced by the anterior pituitary gland and is responsible for stimulating the development of ovarian follicles in women and for supporting testicular Sertoli cells critical for spermatogenesis in males. In both male and females, FSH secretion is regulated by a balance of positive and negative feedback mechanisms involving the hypothalamic-pituitary axis, the reproductive organs, and the pituitary and sex steroid hormones. Measurement of FSH levels therefore provides insight into the functioning of hypothalamic-pituitary-gonadal axis and is used in the clinical evaluation of infertility (both female and male), menstrual irregularities, pituitary disorders, precocious or delayed puberty, and ovarian/testicular dysfunction. Diseases caused by malfunction of the hypothalamic-pituitary-gonadal axis are varied with wide-ranging impact and affect low-, mid and high-resource countries.

#### Infertility

Evaluating FSH levels is a tool for diagnosing potential causes of infertility. For example, an FSH level may assist in distinguishing a gonadal from a pituitary cause of anovulation or azoospermia as well as provide an indication of ovarian reserve and predicting IVF success (1). Estimates suggest that between 48.5 couples to 186 million women globally are infertile (2,3). Although differing methods and definitions have been used to derive infertility burden, a recent review estimated global prevalence of infertility to be 9% (4). Data on worldwide prevalence of childlessness further estimate that as many as 70 million couples would benefit from medical intervention to achieve pregnancy (5).

We do not have sufficient data to assess global infertility prevalence trends over the past 20 years. However the trends can be impacted by a rise in STIs with subsequent impaired reproductive organ function, lifestyle changes and delayed child bearing (2,3,4).

The economic and social impact of infertility is significant. This is particularly true for infertile women who will often suffer from social isolation, discrimination, disinheritance, depression, abuse, divorce and possible abandonment in old age. Infertility as a common cause of childlessness can also have a negative economic impact on women, men and families in general, particularly in developing countries, where children contribute to generating family income and older parents are dependent on their children for support.

Infertility, which had been viewed as a health issue only in developed countries, has now been recognized as an essential component of reproductive health by The United Nations Programme of Action (6). Paradoxically, nations with the highest overall fertility are also the ones with the greatest prevalence of infertility and these often include LMICs. Given the economic, resource, cultural and religious constraints, infertility services among countries will vary significantly. However, assays that measure serum FSH levels are relatively non-invasive (requiring only a blood draw or finger stick), inexpensive and accessible from laboratories throughout the world.

#### Ovarian Reserve

The number of eggs present in the ovaries (oocytes) is established at birth and declines over time; contrary to spermatogenesis, oocyte regeneration does not occur throughout a woman's lifetime. Ovarian reserve testing can inform women regarding their reproductive lifespan. Confirming the presence of viable oocytes and the potential to ovulate is also useful for female cancer patients of reproductive age who are being treated with gonadotoxic therapy. Although other methods (such as Antimüllerian hormone and antral follicular count) exist (7), measuring FSH levels at pre-determined times of her menstrual cycle, typically day 3, remains an important test for evaluating ovarian reserve in sub-fertile women (8). Although single measurements of FSH are not predictive of the peri-menopausal state or the timing of menopause, elevated FSH levels may be used to confirm menopausal status (9), particularly in women who have had prior hysterectomies (with ovaries intact) and in whom the absence of menses cannot be used as a reliable indicator of ovarian function.

#### Menstrual Disorders

FSH levels can also be used in the evaluation of irregular menstrual bleeding, particularly oligomenorrhea and amenorrhea, by helping to distinguish ovulatory dysfunction from uterine abnormalities as the cause. Estimates of menstrual disorders range from 5% to ~36% (10) and occurrence is dependent on age, nutritional status and country of residence.

Polycystic ovarian syndrome (PCOS) represents a subset of menstrual irregularity. It is thought to be the most common endocrine disorder found in women of reproductive age (11) and impacts all races and ethnicities. In unspecified populations the prevalence of PCOS has a reported incidence rate of 3–10%, although more precise incidence is unknown due to under-diagnosis. Common symptoms of PCOS include irregular menstrual cycle, polycystic ovaries, and hirsutism (12), but may also include infertility, insulin-resistance, impaired glucose tolerance (Type 2 Diabetes) and dyslipidemia (12). Multiple diagnostic criteria have been adopted for PCOS, but the common denominator appears to be oligoovulation and androgen excess.

#### Gonadal Dysfunction

Gonadal dysfunction can also be evaluated by measurement of FSH levels to distinguish between primary gonadal failure (hypergonadotropic) and deficient gonadal stimulation (hypogonadotropic hypogonadism) (13).

In females with hypergonadotropic hypogonadism the most common cause is Turner syndrome, which has an incidence of 1 case per 2,500 live births (14). In males with hypergonadotropic hypogonadism, the most common cause is Klinefelter syndrome, which has an incidence of 1 case per 1000 live births (12). Hypogonadotropic hypogonadism is more rare.

Children with hypogonadism experience delayed puberty if left untreated. Timely diagnosis of hypogonadism allows treatment with prepubertal hormone replacement (14). For girls, administration of oestrogen allows for emergence of secondary sex characteristics as well as adequate breast and uterine development. In addition, treatment with human growth hormone, if initiated early on, may increase height significantly. For boys, testosterone administration is used to induce puberty (14)

Measurement of FSH can also aid in the diagnosis of suspected precocious puberty (PP) (15). The overall incidence of PP is estimated to be 1:5,000 to 1:10,000 children and occurs in females at ten times the frequency as in males (15). Gonadotropin-independent precocious puberty is about one fifth as common as gonadotropin-dependent precocious puberty (15). In addition to the negative psychosocial impact associated with PP, the premature pubertal growth spurt and the accelerated bone maturation result in reduced adult height (15).

#### References

1. Taylor A. ABC of sub-fertility: Making a diagnosis. *BMJ* 2003;327(7413):494–7.
2. Mascarenhas MN1, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Med.* 2012;9(12):e1001356. doi: 10.1371/journal.pmed.1001356.
3. Rutstein SO, Shah IH (2004) Infecundity, infertility, and childlessness in developing countries. Calverton (Maryland): ORC Macro.
4. Boivin J, Bunting L, Collins JA, Nygren KG (2007) International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod* 22: 1506–1512.
5. Ombelet W. Is global access to infertility care realistic? The Walking Egg Project. *Reprod Biomed Online.* 2014;28(3):267-72.
6. Nachtigall RD. International disparities in access to infertility services. *Fertility and Sterility* 2006; 85(4): 871-75.
7. American College of Obstetricians and Gynecologists Committee Opinion Number 781. Infertility Workup for Women's Health Specialists. *Obstet Gynecol* 2019;133,(6):e377-84.
8. Testing and interpreting measures of ovarian reserve: A Committee Opinion Practice Committee of the American Society for Reproductive Medicine, Birmingham, Alabama *Fertil Steril* 2015;103:e9–e17.
9. Polesel DN, Nozoe KT, Sanchez MZ et al. The Follicle-Stimulating Hormone as Best Classifier for Diagnosis of Natural Menopause. *J Gynecol Surg* 2017;33(6):236-42.
10. Kwak Y, Kim Y, Baek KA. Prevalence of irregular menstruation according to socioeconomic status: A population-based nationwide cross-sectional study. *PLoS ONE* 2019;14(3): e0214071.
11. Wolf WM, Wattick RA, Kinkade ON, Olfert MD. Geographical prevalence of polycystic ovary syndrome as determined by region and race/ethnicity. *Int J Environ Res Public Health.* 2018; 15(11):2589.
12. Taylor HS, Pai L, Seli E. Speroff's Clinical Gynecologic Endocrinology and Infertility. 9th Ed. Philadelphia, PA: Wolters Kluwer; 2019: 411-417.
13. Fleseriu M, Hashim IA, Karavitaki N et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinology & Metabolism*; 101(11); 3888–3921
14. Viswanathan V, Eugaster EA. Etiology and Treatment of Hypogonadism in Adolescents. *Pediatr Clin North Am.* 2011; 58(5): 1181–xx.
15. Sinha SK, Hoffman RP. Precocious Pseudopuberty. <https://emedicine.medscape.com/article/923876-overview#a6>.

## 8. Potential public health impact of the test:

Please explain in which way the proposed test benefits public health. Please detail your response and add references:

#### Infertility

Measurement of FSH levels is usually included in a basic infertility workup, generally as part of a panel of reproductive markers. Elevated FSH levels can indicate decreased ovarian function and consequent anovulation as well as insufficient ovarian reserve. FSH levels measured on menstrual cycle days 2, 3, 4 can also be used in evaluation whether an IVF cycle will be successful, although the sensitivity for predicting poor response is highly variable and dependent on the cutpoint. The sensitivity for predicting failure to achieve pregnancy is poorer (16).

FSH levels may also be useful in predicting diminished ovarian reserve in response to a clomiphene challenge. Studies have indicated that measurement of FSH levels after a clomiphene challenge is less specific than basal FSH but results in increasing specificity (17). The knowledge that an IVF cycle is likely to be unsuccessful can have a cost-saving impact on management and may also help alleviate the disappointment and stress that couples experience when assisted reproduction fails.

#### Menstrual Disorders

Irregular menses, particularly amenorrhea and oligomenorrhea, are generally indicative of a defect at some point in the hypothalamic-pituitary-ovarian-uterine axis and FSH levels are utilized in evaluating the etiology. Elevated FSH levels are an indication of ovarian dysfunction or failure, while normal or low levels suggest pituitary or hypothalamic failure (18).

Confirmation that irregular menstrual bleeding is caused by hypothalamic-pituitary-ovarian dysfunction allows corrective treatment with hormonal intervention and carries a high degree of success in regulating cycles. In addition, appropriate hormonal replacement will aid in preventing the sequelae of oestrogen deficiency.

#### PCOS

An elevated ratio of LH to FSH (greater than 3) is often used in conjunction with history and physical exam to support a diagnosis of PCOS, a syndrome that falls into the category of menstrual disorders (19). Appropriate diagnosis of PCOS allows hormonal treatments that can regulate menstrual cycles, induce ovulation when indicated, decrease androgenic effects and also reduce the risks of metabolic abnormalities that frequently occur with PCOS.

#### Gonadal Dysfunction

Exogenous administration of GnRH is often used to differentiate primary gonadal failure (hypergonadotropic) and deficient gonadal stimulation (hypogonadotropic hypogonadism) (20). Following administration of exogenous GnRH, FSH levels will be totally or partially absent in hypogonadotropic hypogonadism but will gradually appear in response to the exogenous GnRH in hypergonadotropic hypogonadism. Children with hypogonadism will experience delayed puberty if left untreated. Timely diagnosis of hypogonadism allows treatment with prepubertal hormone (sex steroid) replacement (21). For girls, administration of oestrogen allows for emergence of secondary sex characteristics as well as adequate breast and uterine development. In addition, treatment with human growth hormone, if initiated early on, may increase height significantly. For boys, testosterone administration is used to induce puberty (21).

Measurement of FSH after GnRH stimulation can also aid in the diagnosis of suspected precocious puberty (22). An increase in FSH levels in response to a GnRH challenge is indicative of central precocious puberty (gonadotropic-dependent), while no increase supports a diagnosis of peripheral (gonadotropic-independent) precocious puberty. Early diagnosis of central precocious puberty allows for treatment with GnRH agonists that can delay the onset of puberty until a more appropriate age. The psychosocial and physical burdens of undiagnosed and untreated delayed or precocious puberty are significant and it is important that all tools to aid in a timely diagnosis be available.

#### References

16. [?] Testing and interpreting measures of ovarian reserve. A Committee Opinion. Practice Committee of the American Society of Reproductive Medicine, Birmingham, Alabama. Fertil Steril 2015;103:e9-17.

17. [?] Hendriks DJ, Mol BW, Bancsi LF, te Velde ER, Broekmans FJ. The clomiphene citrate challenge test for the prediction of poor ovarian response and nonpregnancy in patients undergoing in vitro fertilization: a systematic review. Fertil Steril. 2006 Oct;86(4):807-18. Epub 2006 Sep 7.

18. [?] Taylor HS, Pai L, Seli E. Speroff's Clinical Gynecologic Endocrinology and Infertility. 9th Ed. Philadelphia, PA: Wolters Kluwer; 2019: 399.

19. [?] Hsu M, Liou TH, Liang SJ. Inappropriate gonadotropin secretion in polycystic ovary syndrome. Fertility and Sterility 2009;91(4):1168-74.

20. [?] Fleseriu M, Hashim IA, Karavitaki N et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinology & Metabolism; 101(11); 3888–3921

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21. [?] Viswanathan V, Eugaster EA. Etiology and Treatment of Hypogonadism in Adolescents.  
Pediatr Clin North Am. 2011; 58(5): 1181-xx.

22. [?] Kaplowitz PB, Hoffman RP. What is the role of gonadotropin testing in the diagnosis of precocious puberty?  
<https://www.medscape.com/answers/924002-95756/what-is-the-role-of-gonadotropin-testing-in-the-diagnosis-of-precocious-puberty>

## 9. Clinical utility of the proposed test/potential impact of the test on patient management and care

Please provide your answer as described in the guidance document:

The measurement of FSH levels, often in combination with other tests, is utilized in reaching the diagnosis of multiple diseases and syndromes in the area of reproductive health involving the hypothalamic-pituitary-gonadal axis.

In the evaluation and management of infertility, FSH levels provide insight into ovarian reserve and in predicting the success of IVF. This information can be used to guide decisions as to whether to proceed with an IVF cycle and will in turn contribute to controlling overall cost. Although AMH has gained favour for these purposes (23), FSH is a less expensive and more accessible test; it will therefore provide a more reasonable choice as infertility services (including IVF) are introduced into LMICs.

Results from FSH levels can aid in the evaluating the cause of menstrual irregularities by indicating whether ovulation has occurred (24).

In cases of anovulatory amenorrhea, FSH levels provide information as to whether the defect in the hypothalamic-pituitary-ovarian (HPO) axis is gonadal or central. When hypogonadism is confirmed by high FSH levels as in premature ovarian insufficiency (POI) or natural menopause, the sequelae of oestrogen deficiency can be addressed by hormone replacement, thus reducing significant morbidity.

In the evaluation of primary amenorrhea, high FSH levels provide confirmation of hypogonadism. Early diagnosis of hypogonadal syndromes, such as Turner or Klinefelter syndromes, allows more complete evaluation of anomalies often associated with the syndromes. Furthermore, administration of growth hormone to young girls in childhood and hormone replacement at puberty for both girls and boys can reduce morbidity and mortality, as well as improve the quality of life (25).

Anovulatory or dysfunctional uterine bleeding can impact women's health and well being by causing unscheduled and often excessive bleeding. Measurement of FSH levels is a part of the laboratory investigation to arrive at the diagnosis (26). Once the diagnosis is established, bleeding can be controlled with administration of appropriate hormonal therapy to re-establish the pattern of cyclic endometrial shedding. Morbidity is decreased by reducing the risk of anaemia due to blood loss and endometrial hyperplasia from oestrogen over-stimulation. Economic impact is also lessened by reducing absences from work or school. Likewise, increased social isolation, often directed at menstruating women in LMICs, is avoided as well.

FSH results also facilitate the diagnosis and treatment of PCOS with the short-term benefit of restoring ovulation and HPO balance (27). Equally important are the preventative long-term benefits of reducing the risk of developing diabetes and the metabolic syndrome.

Measurement of FSH levels is also used in diagnosing PP. In gonadotropin-dependent PP, diagnosis of elevated levels allows ruling out adrenal hyperplasia or central nervous system lesions (28). In gonadotropin-independent PP, investigation of the source of exogenous oestrogens can lead to a more timely diagnosis of gonadal hormone-producing cysts or tumors.

Although early diagnosis of disorders of sexual development can reduce morbidity and mortality and improve physical and psychological well being, there is considerable variation in how these disorders are managed in resource-rich and resource-poor countries (29). Since these discrepancies appear to be driven more by poverty than religious or cultural beliefs, general proposals have been set forward to close the gap in how these disorders are addressed: establishing specialized treatment centers, development of diagnostic algorithms for low-resource settings, improving laboratory quality assurance and assuring availability of appropriate medications for treatment. If implemented in LMICs, these proposals are will improve management once the diagnosis of sexual development disorders is established (29).

## References

23. Tal R, Seifer DB. Ovarian reserve testing: a user's guide. *American J Obstet Gynecol* 2017; 217(2):129–40.

24. Taylor HS, Pai L, Seli E. *Speroff's Clinical Gynecologic Endocrinology and Infertility*. 9th Ed. Philadelphia, PA: Wolters Kluwer; 2019:399.

25. Viswanathan V, Eugaster EA. Etiology and Treatment of Hypogonadism in Adolescents. *Pediatr Clin North Am*. 2011; 58(5): 1181–xx.

26. Taylor HS, Pai L, Seli E. *Speroff's Clinical Gynecologic Endocrinology and Infertility*. 9th Ed. Philadelphia, PA: Wolters Kluwer; 2019:396.

27. Hsu M, Liou TH, Liang SJ. Inappropriate gonadatropic secretion in polycystic ovary syndrome. *Fertility and Sterility* 2009;91(4):1168-74.

28. Taylor HS, Pai L, Seli E. *Speroff's Clinical Gynecologic Endocrinology and Infertility*. 9th Ed. Philadelphia, PA: Wolters Kluwer; 2019:326.

29. Warne GW, Raza J. Disorders of sex development (DSDs), their presentation and management in different cultures. *Rev*

## 10. Systematic reviews of the clinical accuracy of the test

Please describe or comment as requested in guidance document or state if no systematic review of clinical accuracy studies exists:

Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update. 2006;12(6):685–718.

This is a large systematic review (37 studies) evaluating clinical accuracy to predict IVF outcomes. Variability in sensitivity was observed, and was highly dependent on the FSH cutpoint threshold chosen. For FSH cutpoints less than 10 IU/L, sensitivity to predict poor outcome ranged from 65% to 100% with specificity from 5% to 100%. Positive likelihood ratios for a positive result using the lower FSH cutpoint ranged from 1.1 to 4.4 IU/L. For FSH cutpoints less than 10 IU/L, sensitivity to predict non-pregnancy ranged from 26% to 78% with specificity from 27% to 87%. Positive likelihood ratios for a positive result using the lower FSH cutpoint from ranged from 1.1 to 6.8 IU/L.

The authors conclude that basal FSH may be adequate for predicting poor response and non-pregnancy only at high FSH threshold levels. Further, it may not be suitable as a diagnostic test to exclude patients from undergoing IVF, but more as a screening test for counselling patients and in determining further diagnostic steps.

Despite the review's limited support for the use of basal FSH levels in assisted reproductive procedures, LMICs offering IVF may favour using basal FSH at higher cutpoint levels as it is accessible and less costly than other diagnostic tools for predicting outcome.

Please attach the reviews you make reference to:

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## 11. Primary studies of clinical accuracy of the test

Please describe or comment as requested in the guidance document or state if no primary studies of clinical accuracy are available:

Akande VA, Keay SD, Hunt LP, Mathur RS, Jenkins JM, Cahill DJ. The practical implications of a raised serum FSH and age on the risk of IVF treatment cancellation due to a poor ovarian response. J Assist Reprod Genet. 2004 Jul;21(7):257-62.

Treatment cycles cancelled due to a poor ovarian response to gonadotropins were studied in 536 women undergoing IVF. Modeling demonstrated that high FSH and age were independent predictors of poor response to hyperstimulation and were independently associated with the risk of treatment cancellation.

Creus M, Peñarrubia J, Fábregues F et al. Day 3 serum inhibin B and FSH and age as predictors of assisted reproduction treatment outcome. Hum Reprod. 2000 Nov;15(11):2341-6.

120 women undergoing assisted reproductive technology, including 40 consecutive cycles cancelled due to poor follicular response, were studied. The association of basal FSH (with an accuracy or predictive value of ovarian response of 79%) with cancellation rate was significant with a predictive value of 79% and was independent of and stronger than the effects of age and inhibin B ( $P < 0.05$ ). Basal FSH concentration was a better predictor of cancellation rate than age, but age was a stronger predictor of pregnancy rate.

Please attach the publications you make reference to:

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## 12. Systematic reviews of the clinical utility/impact of the test on patient management and care

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| Please describe any systematic reviews of studies on the impact of the test result in clinical practice on diagnosis, treatment and patient outcomes or state if none are available (please refer to the guidance document)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Hypothalamic-Pituitary-Ovarian Axis Disorders Impacting Female Fertility<br>Mikhael S, Punjala-Patel A, Gavrilova-Jordan L. Biomedicines. 2019 Mar;7(1): 5.<br>Published online 2019 Jan 4.<br><br><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6466056/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6466056/</a><br><br>This review discussed that in general, basic evaluation of hypothalamic-pituitary failure includes measurement of FSH (with LH and oestradiol [E2]).<br><br>Overall management of hypothalamic-pituitary failure will depend on patient needs. For example, in young women of reproductive age where FSH levels (with E2) are used to diagnose ovarian insufficiency, management can include reassurance and education regarding alternate reproductive options currently available. This may also apply to patients with mosaic Turner syndrome who become aware of impending follicular atresia and who wish to preserve fertility through oocyte or embryo cryopreservation.<br><br>In cases where ovarian failure is confirmed, either premature or due to natural menopause, the diagnosis allows for monitoring the effects of oestrogen deficiency and consideration of hormonal replacement to prevent or delay the associated morbidity. |
| Please attach the reviews you make reference to:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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## 13. Primary studies of the clinical utility/impact of the test on patient management and care

Please briefly describe any primary studies of the clinical utility/impact of the test on patient management and care, or state if none are available (please refer to the guidance document):

**Infertility:**

Eijkimans MJ, Imani B, Mulders AG, Habbema JD, Fauser BC. High singleton live birth rate following classical ovulation induction in normogonadotrophic anovulatory infertility (WHO 2). *Hum Reprod.* 2003 Nov;18(11):2357-62

All patients commenced with clomiphene for ovulation induction; those who did not ovulate within three treatment cycles of incremental daily doses up to 150 mg for 5 consecutive days or ovulatory CC patients who did not conceive within six cycles, subsequently underwent gonadotropin induction of ovulation applying a step-down dose regimen.

Of 240 consecutive women, there were 134 pregnancies ending in a singleton live birth (56% of women). The cumulative pregnancy rate after 12 and 24 months of follow-up was 50% and 71% respectively. Conclusion: Classical ovulation induction produces very good results in normogonadotrophic anovulatory infertility.

**Menstrual irregularities/Anovulation**

Hurskainen R, Teperi J, Rissanen P, Aalto AM, Grenman S, Kivela A, et al. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up. *JAMA* 2004;291:1456-63.

There is general acceptance throughout the clinical community that hormonal therapy is highly successful in treating DUB. This study followed over 200 women with DUB who were treated with a triphasic preparation of norgestimate and ethinyl E2. Greater than 80% were documented to have improvement in bleeding and this was significantly increased over the placebo group. Conclusion: The triphasic combination of norgestimate and ethinyl E2 is an effective treatment for metrorrhagic, menometrorrhagic, oligomenorrheic, and polymenorrheic dysfunctional uterine bleeding.

**General Reproductive Function**

Linglart A, Cabrol S, Berlier P, Stuckens C, Wagner K, de Kerdanet M, Limoni C, Carel JC, Chaussain JL; French Collaborative Young Turner Study Group. Growth hormone treatment before the age of 4 years prevents short stature in young girls with Turner syndrome. *Eur J Endocrinol.* 2011 Jun;164(6):891-7. doi: 10.1530/EJE-10-1048.

64 young girls were treated with recombinant growth hormone. After 4 years a gain in mean height was observed compared to a decrease in mean height in the control group. Conclusion: Early treatment with growth hormone helps to prevent natural evolution towards short stature in most girls with Turner syndrome.

Lee PA1, Klein K, Mauras N, Neely EK, Bloch CA, Larsen L, Mattia-Goldberg C, Chwalisz K.

Efficacy and safety of leuprolide acetate 3-month depot 11.25 milligrams or 30 milligrams for the treatment of central precocious puberty. *J Clin Endocrinol Metab.* 2012 May;97(5):1572-80. doi: 10.1210/jc.2011-2704

76 girls with PP were treated with leuprolide acetate, a GnRH agonist every 3 months. At 6 months 98% exhibited LH suppression and 100% estradiol suppression. Conclusion: Treatment with leuprolide acetate 3-month depot formulations (11.25 and 30 mg) effectively suppressed the GnRH axis.

Please include the articles/documents of key primary studies and all publications you make reference to:

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## 14. Details of any guideline recommendations concerning use of the test

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| <p>Briefly describe the specific recommendation (indicate where it can be found in the guideline) and summarise the evidence upon which it is based (indicating where it can be found in the evidence summaries):</p> <p>Central hypogonadism: Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. Fleseriu M, Hashim IA, Karavitaki N et al. The Journal of Clinical Endocrinology &amp; Metabolism 20216;101(11):3888–3921.</p> <p><a href="https://academic.oup.com/jcem/article/101/11/3888/2764912">https://academic.oup.com/jcem/article/101/11/3888/2764912</a></p> <p>1.14 In the presence of oligomenorrhea or amenorrhea, we recommend measuring serum estradiol (E2), FSH, and LH.</p> <p>1.12 In males with suspected hypogonadism, we recommend measuring serum T, FSH, and LH to diagnose central hypogonadism.</p> <p>Amenorrhea: ACOG Committee Opinion Number 605, July 2014.</p> <p>Box 1. Diagnosis and Initial Evaluation of Primary Ovarian Insufficiency</p> <p>Diagnosis of primary ovarian insufficiency</p> <ul style="list-style-type: none"> <li>• Menstrual irregularity for at least 3 consecutive months</li> <li>• Follicle-stimulating hormone and estradiol levels (two random tests at least 1 month apart)</li> </ul> <p><a href="https://www.ncbi.nlm.nih.gov/pubmed/24945456">https://www.ncbi.nlm.nih.gov/pubmed/24945456</a></p> <p>Ovarian Reserve: Testing and interpreting measures of ovarian reserve: A Committee Opinion</p> <p>Practice Committee of the American Society for Reproductive Medicine, Birmingham, Alabama <a href="https://www.asrm.org/globalassets/s/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/testing_and_interpreting_measures_of_ovarian_reserve_a_committee_opinion-noprint.pdf">https://www.asrm.org/globalassets/s/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/testing_and_interpreting_measures_of_ovarian_reserve_a_committee_opinion-noprint.pdf</a></p> <p>Page e2: Despite its limitations, FSH is commonly used as a measure of ovarian reserve, and high values have been associated with, but do not necessarily predict, both poor ovarian stimulation and the failure to conceive.</p> <p>Page e4: In summary, a single FSH value has very limited reliability because of inter- and intra-cycle variability (particularly if it is not elevated). An elevated FSH value has good specificity but may represent a false positive especially when used in a low-risk population. Given the inter-assay variability of FSH, the cutpoint selected by an IVF program ideally should be based on its own data or on data from studies using the same FSH assay.</p> <p>ACOG Committee Opinion Primary Ovarian Insufficiency in Adolescents and Young Women Number 605 • July 2014</p> <p><a href="https://www.acog.org/-/media/Committee-Opinions/Committee-on-Adolescent-Health-Care/co605.pdf?dmc=1&amp;ts=20191101T0240323417">https://www.acog.org/-/media/Committee-Opinions/Committee-on-Adolescent-Health-Care/co605.pdf?dmc=1&amp;ts=20191101T0240323417</a></p> <p>Page 2: Initial laboratory evaluation for suspected primary ovarian insufficiency includes measurements of basal FSH and basal estradiol levels and tests to rule out causes such as pregnancy, thyroid disease, and hyperprolactinemia... If gonadotropins are elevated into the menopausal range (typically, basal FSH levels will be greater than 30 – 40 mIU/mL, depending on the laboratory used), a repeat FSH measurement is indicated in 1 month. If the result indicates that FSH is elevated, a diagnosis of primary ovarian insufficiency can be established.</p> <p>Box 1: Diagnosis of primary ovarian insufficiency</p> <ul style="list-style-type: none"> <li>• Menstrual irregularity for at least 3 consecutive months</li> <li>• Follicle-stimulating hormone and estradiol levels (two random tests at least 1 month apart)</li> <li>• Prolactin and thyroid function test</li> </ul> |
| <p>Please attach the guidelines that you are referring to:</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <p>filecount - Please attach the guidelines that you are referring to:</p> <p>0</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

## 15. Examples of commercially available IVD products in the proposed new category

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Please download and complete the table in Annex I with commercially available IVD products in the test category, and include the information listed for each one. Please upload the completed file back and all the relevant test Instructions For Use (Package Inserts):</p> |
| <pre>[{"title":"Commercial FSH Tests","comment":"","size":"44.156","name":"Annex%20I%20-%20WHO.FSH%20Full%20submission.docx","filename":"fu_iqar9dxd3zubnmq","ext":"docx"}]</pre>                                                                                                |

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filecount - Please download and complete the table in Annex I with commercially available IVD products in the test category, and include the information listed for each one. Please upload the completed file back and all the relevant test Instructions For Use (Package Inserts):

1

## 16. Training requirements

Considering the tests mentioned in 15 above, what in general are the training requirements?:

Certification for use

## 17. Equipment required

Considering the tests mentioned in 15 above, please describe in general terms what, if any, equipment is required other than that provided with the test:

Refrigerator, pipettes, racks, uninterrupted power source, running water.

## 18. Energy requirements

Considering the tests mentioned in 15 above, what, if any energy source is required for performance of the tests?:

Continuous electrical power

Considering the tests mentioned in 15 above, what, if any energy source is required for performance of the tests?: [Other]

## 19. Landscape reviews

Please list any landscape reviews describing the different test technologies and their use or state if none available:

None available

Please attach the documents referred to in this question:

filecount - Please attach the documents referred to in this question:

0

## 20. Cost and Cost-effectiveness

Please provide a summary of data on comparative cost and cost-effectiveness or state if not available:

Infertility: By comparison, the cost (in USD) of a FSH test in the US is ~\$23, in India \$4.00 -10.00, in AU \$22 and \$34 in Uganda. Prices among manufacturers are competitive and will not likely be significantly different. By contrast, an AMH test is ~\$100 USD in US, \$17-28 in India, \$64 in Australia and \$80.50 in Uganda. Ultrasound determination of follicle number and size to predict IVF success will be several times more costly than the FSH measurement.

In terms of cost effectiveness, if a FSH measurement is used to predict the success of a cycle of assisted reproductive technology and the results prompt abandoning the cycle, it could result in significant savings (thousands of dollars in the US).

A FSH measurement is also an inexpensive test that can determine whether anovulation has occurred, particularly in cases of amenorrhea. Given the significant syndromes and health issues that are associated with anovulation, such as disorders of sexual development or PCOS, there should be no question that confirming anovulation and reducing its morbidity would be cost effective.

Identifying anovulatory women also allows preventative measures to be undertaken, for example in addressing oestrogen deficiency or the metabolic sequelae of untreated chronic anovulation. The cost of osteoporotic fractures, that are increased in the hypoestrogen state, is estimated to be 37 billion EUR per year in the EU, and 19 billion USD per year in the USA (International Osteoporosis Foundation <http://www.iofbonehealth.org>). Estimates of the cost of diabetes and metabolic syndrome are less definable, but identification of those at risk and taking preventative measures should offset the cost of measuring reproductive hormone levels when the diagnosis is suspected.

## 21. Ethical issues

Please detail any important ethical considerations related to the proposed test category and any consequences of its use:

FSH measurement plays a significant role in the diagnosis and management of infertility, particularly as it relates to assisted reproductive technology. However, infertility may not be assigned a high priority in LMIC healthcare systems. To address this issue, the WHO recommended in 2001 that infertility be viewed as a world health problem and encouraged the development of lower cost assisted reproductive technology. Progress toward this end needs to be accelerated before the full potential of FSH as an infertility diagnostic test can be appreciated.

FSH levels are also used to identify disorders of sexual development attributable to hypogonadism, and identification of these disorders is essential to prevent the sequelae and accompanying morbidity. However, the resources to enable replacement of deficient hormones or to provide treatment to decrease the overall morbidity must be available even in LMICs. Likewise, identifying PP should carry with it the obligation to provide treatment that delays puberty.

## 22. Equity and human rights issues

Please indicate if it reduces inequities and increases accessibility or if the test may prove inaccessible to some populations:

Measurement of FSH levels should be accessible to most global populations. Its use will reduce inequalities, provided that health care systems are both equipped and prepared to follow through and make available the treatments that are indicated by the results.

## Signature

Through the electronic signature below, I acknowledge that I have provided appropriate information to support this submission. I acknowledge that WHO reserves the right to format and select the information provided as necessary and agree that the information will be publicly disclosed by WHO. [Electronic Signature (type your full name to sign):]

Rita Kabra

Through the electronic signature below, I acknowledge that I have provided appropriate information to support this submission. I acknowledge that WHO reserves the right to format and select the information provided as necessary and agree that the information will be publicly disclosed by WHO. [Date (yyyy-mm-dd):]

2019-12-21