Anti-Mullerian Hormone
(抗穆氏管荷爾蒙)的運用

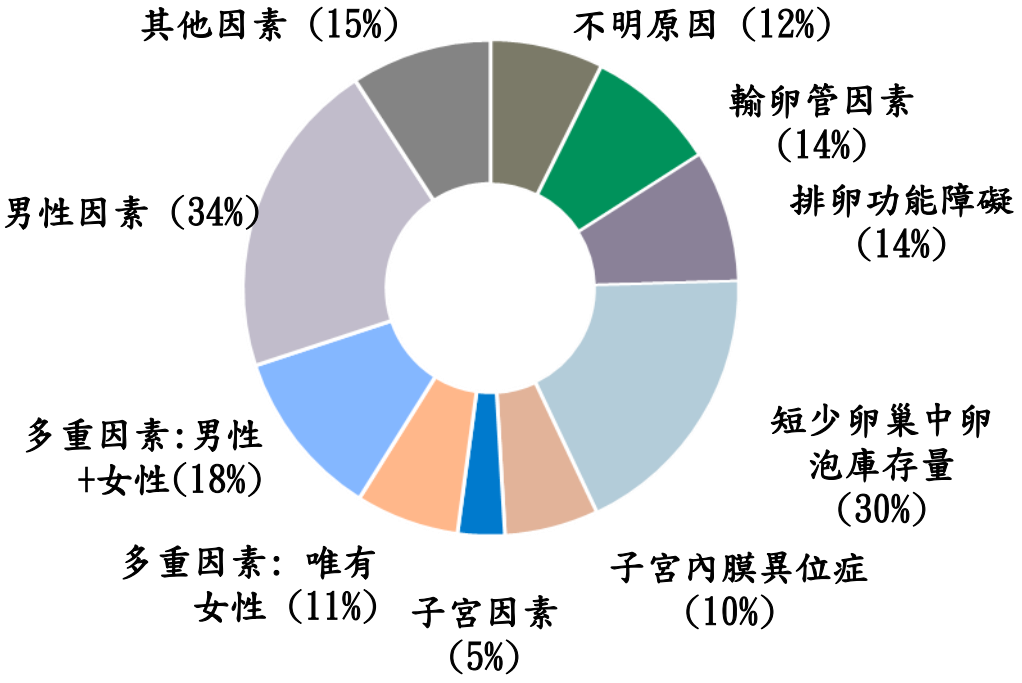
台灣羅氏醫療設備股份有限公司

不孕症的原因

WHO對不孕症的定義

一般稱為不孕症，係夫妻結婚之後，有正常的性行為關係，而且沒有採取任何避孕的措施，超過一年以上，仍然沒有懷孕的跡象，稱之為不孕症

男性和女性因素相同地導致不孕症



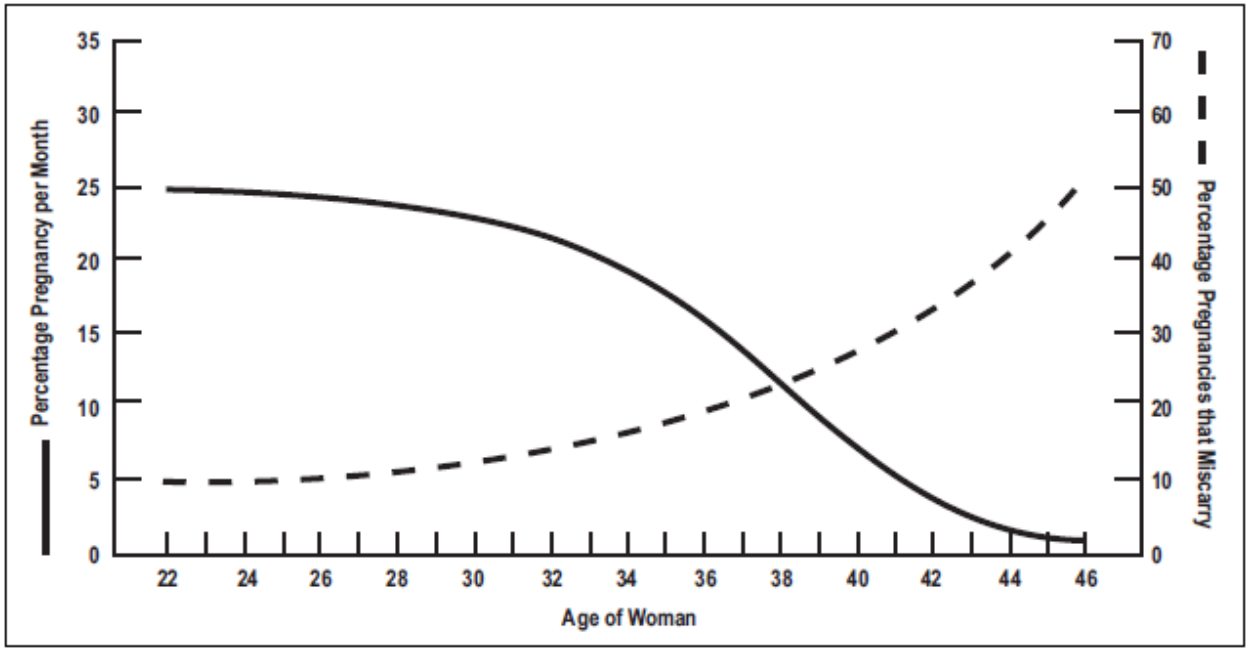
11%的生育年齡的婦女有不孕症不孕症

>1 因素占25%有不孕症問題的夫婦

單獨是男性因素占34%有不孕症問題的夫婦

什麼因素導致生殖力下降?

年齡因素與生殖力下降	• 女性從32歲起生殖力下降 37歲後生殖力更快速下降 • 懷孕率35歲後下降，並伴有流產率增加，自然流產，妊娠並發症及不良懷孕結果



1. ACOG Committee Opinion No. 589. Fertil Steril 2014;101:633–634.
2. Johnson JA et al. J Obstet Gynaecol Can 2012;34:80–93.

調查不孕的原因

婦產科及生殖醫學診所

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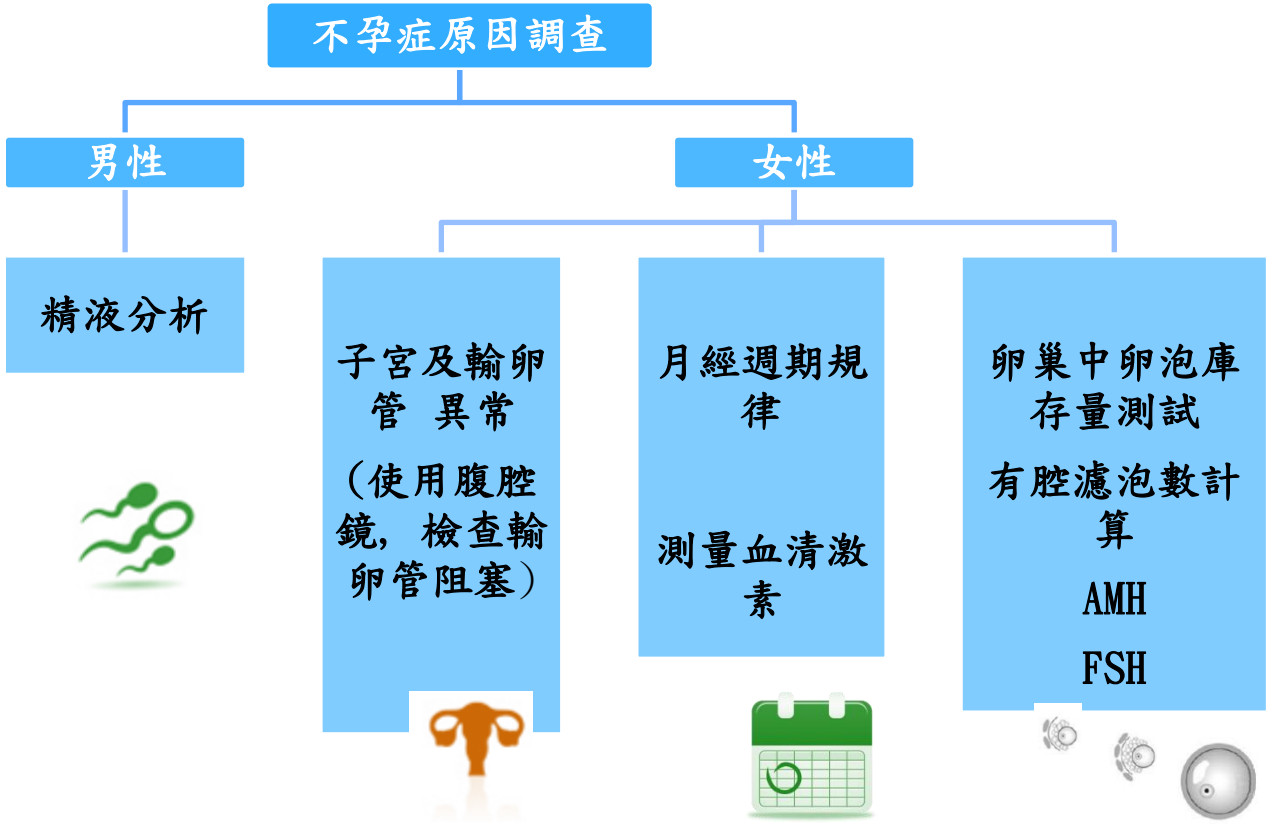

National Institute for Health and Clinical Excellence. Fertility: assessment and treatment for people with fertility problems (February 2013). NICE Clinical Guideline. Available at: http://www.nice.org.uk/nicemedia/live/14078/62770/62770.pdf (Last accessed June 2014).

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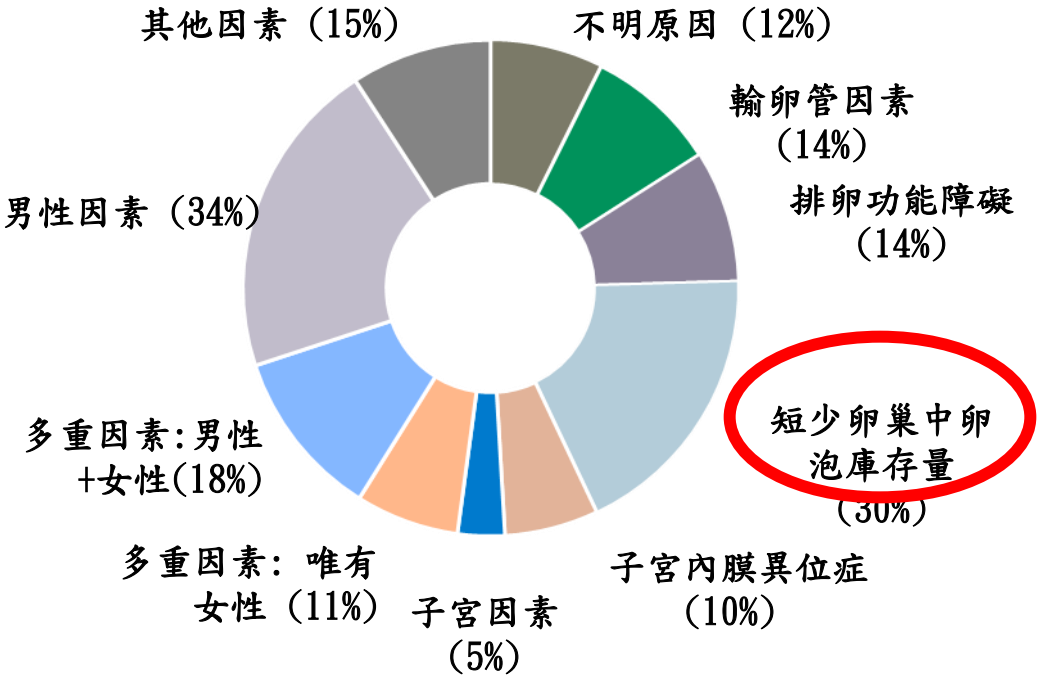

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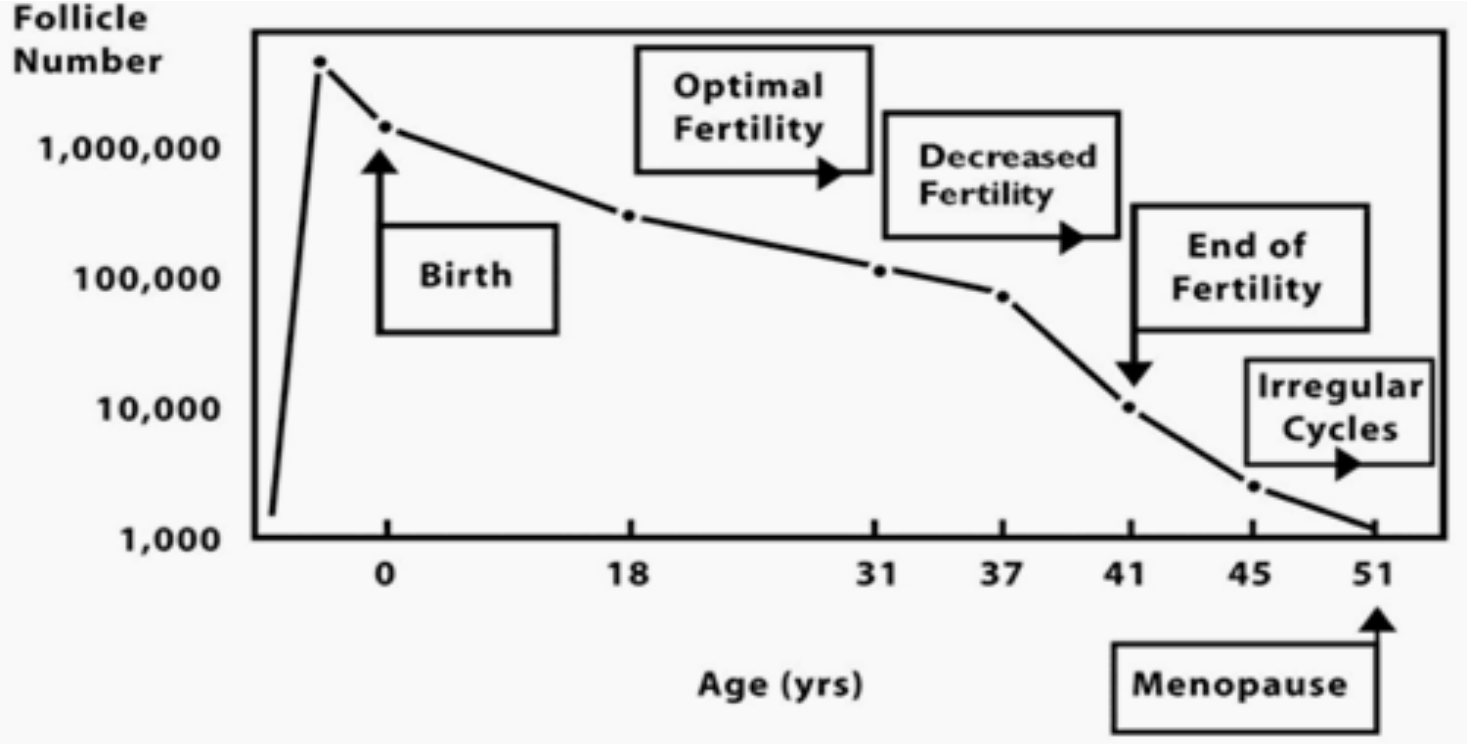
什麼是卵巢中卵泡庫存量?

卵巢中卵泡庫存量是一個用語: 用於確定卵巢的能力，以提供卵細胞，其能夠受精產生了健康和成功懷孕

關鍵訊息 –卵巢儲備急劇下降隨著年齡的增長而降低生育能力

– 在出生時卵巢裡的卵泡的大小數量及下降幅度因人而異



Adapted from: Te Velde ER, et al. *Mol Cell Endocrinol* 1998;145(1–2):67–73.

Maheshwari A, et al. *Hum Reprod* 2006;21(11):2729–35.

目前評估卵巢內卵子庫存量的方法

月經週期第3天*FSH	月經週期第3天 *E_2	超音波（AFC）
	Link to ovarian reserve	
• 增高濃度觀察卵泡耗竭（較長生育年齡）	• 在月經週期中早期昇高是生殖衰老的一個典型特徵	• AFC對於卵巢反應是直接定量指標，並強烈相關與剩餘的原始卵泡庫存量
	限制	
• 月經週期內/間的變異大 • 正常濃度，不能排除卵巢庫存量下降 • 只在月經週期的第2-4天可測	• 月經週期內/間的變異大 • 不能確認卵巢庫存量下降 • 只在月經週期的第2-4天可測	➢ 月經週期內/間的變異大 ➢ 不同操作者的變異大

卵巢儲備功能的超音波標誌物

有腔濾泡數 計算 *(AFC)*

如何連結卵巢內卵子的庫存量?

- AFC 與剩餘的原始濾泡數目有相關性

如何測量?

- AFC是使用2D 或 3D超音波影像技術來計算兩側卵巢有腔濾泡數目 (2 – 10 mm 直徑)

什麼時候測量?

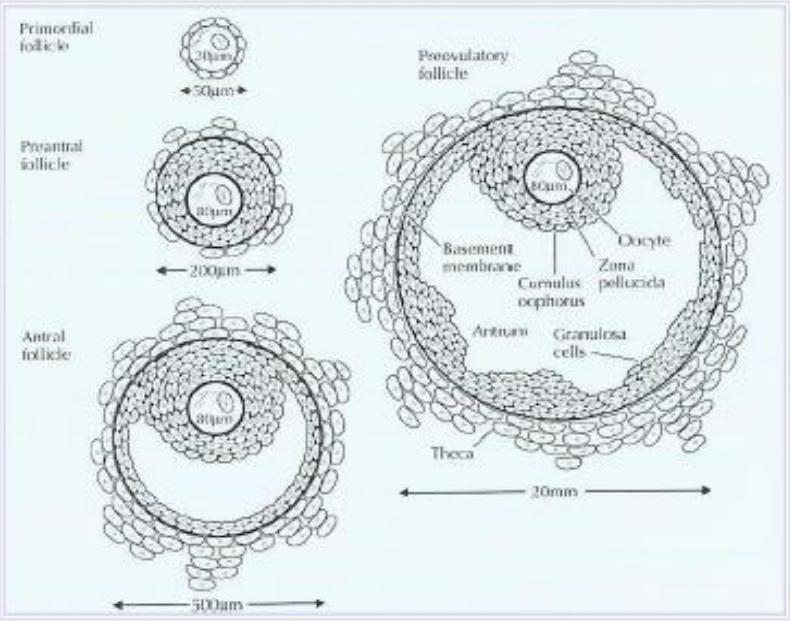
- AFC 被推薦在月經週期(2-4天)的有腔濾泡早期測量, 減少月經週期波動效應的影響

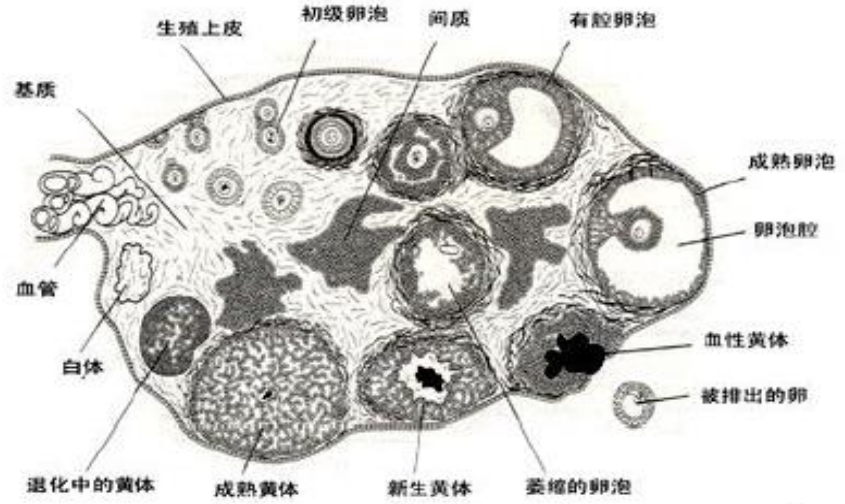
白色箭頭指的是有腔濾泡

Image from: Broekmans et al (2010)

1. Hansen KR et al. Fertil Steril 2011;95:170 – 175.The Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2011;98:1407 – 1415.
2. Nelson SM. Fertil Steril 2013;99:963 – 969.
3. Broekmans FJ et al. Fertil Steril 2010;94:1044 – 1051.

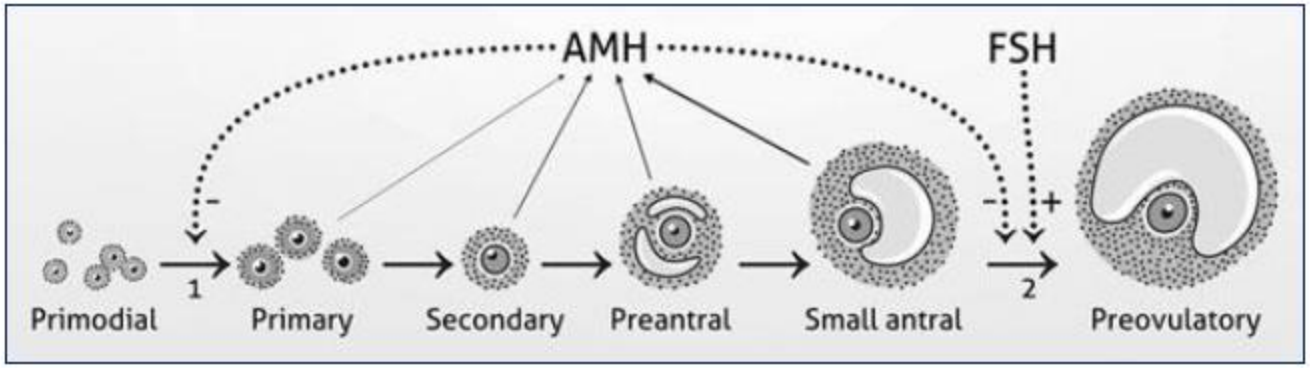
AMH is produced by granulosa cells, from pre-antral and antral follicles.





	濾泡大	卵細胞大小
始基性濾泡 (Primordial follicle)	0.05 mm	25 μm
原發性濾泡 (Primary or Preantral follicle)	2-4 mm	80 μm
室性濾泡 (Antral follicle)	5-10 mm	80 μm
排卵前濾泡 (Preovulatory follicle)	20 mm	80 μm

Anti-Mullerian hormone (AMH) and folliculogenesis



1. AMH inhibits the initial recruitment of primary follicles from the resting pool of primordial follicles (step 1)
2. AMH inhibits the sensitivity of antral follicles to follicle-stimulating hormone (FSH) during cyclic recruitment (step 2).

Acta Obstet Gynecol Scand 2012: 91(11): 1252-60

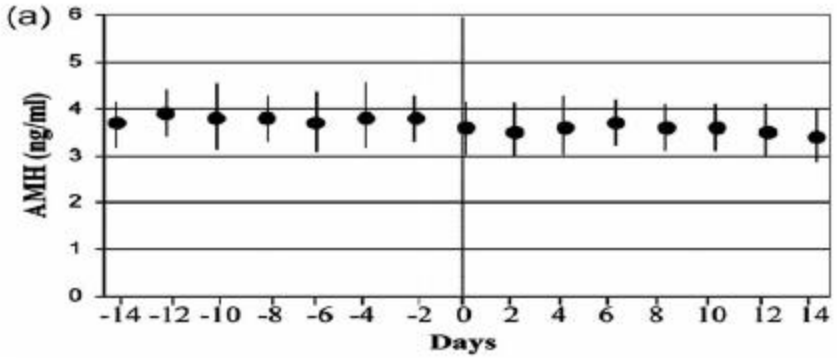
抗穆勒氏管荷爾蒙（AMH）臨床運用

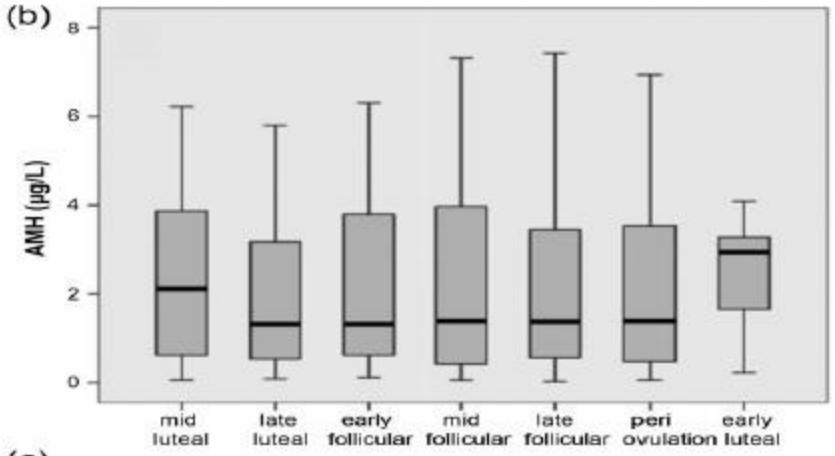
主要適應症 – 在不孕症卵巢中卵泡庫存量的評估

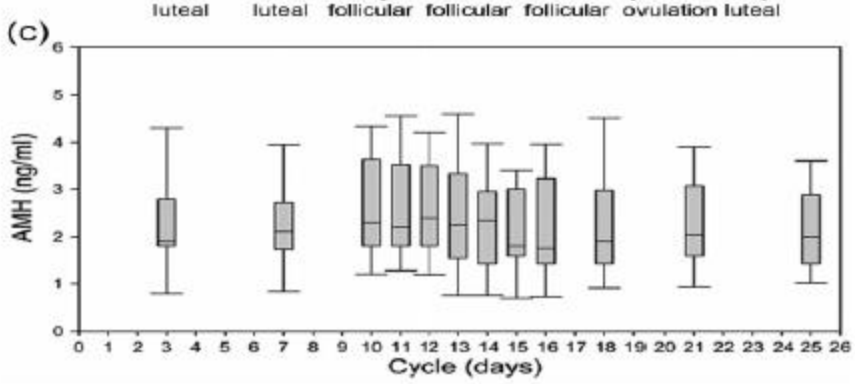
- 循環AMH濃度是反映卵巢中卵泡庫存量儲備能力提供卵子受精

- AMH的血清濃度可以在月經週期期間的任何點進行測定，增加了臨床應用

1. Anderson RA, et al. *Maturitas* 2012;71(1):28–33
2. Nelson SM. *Fertil Steril* 2013;99(4)963–9



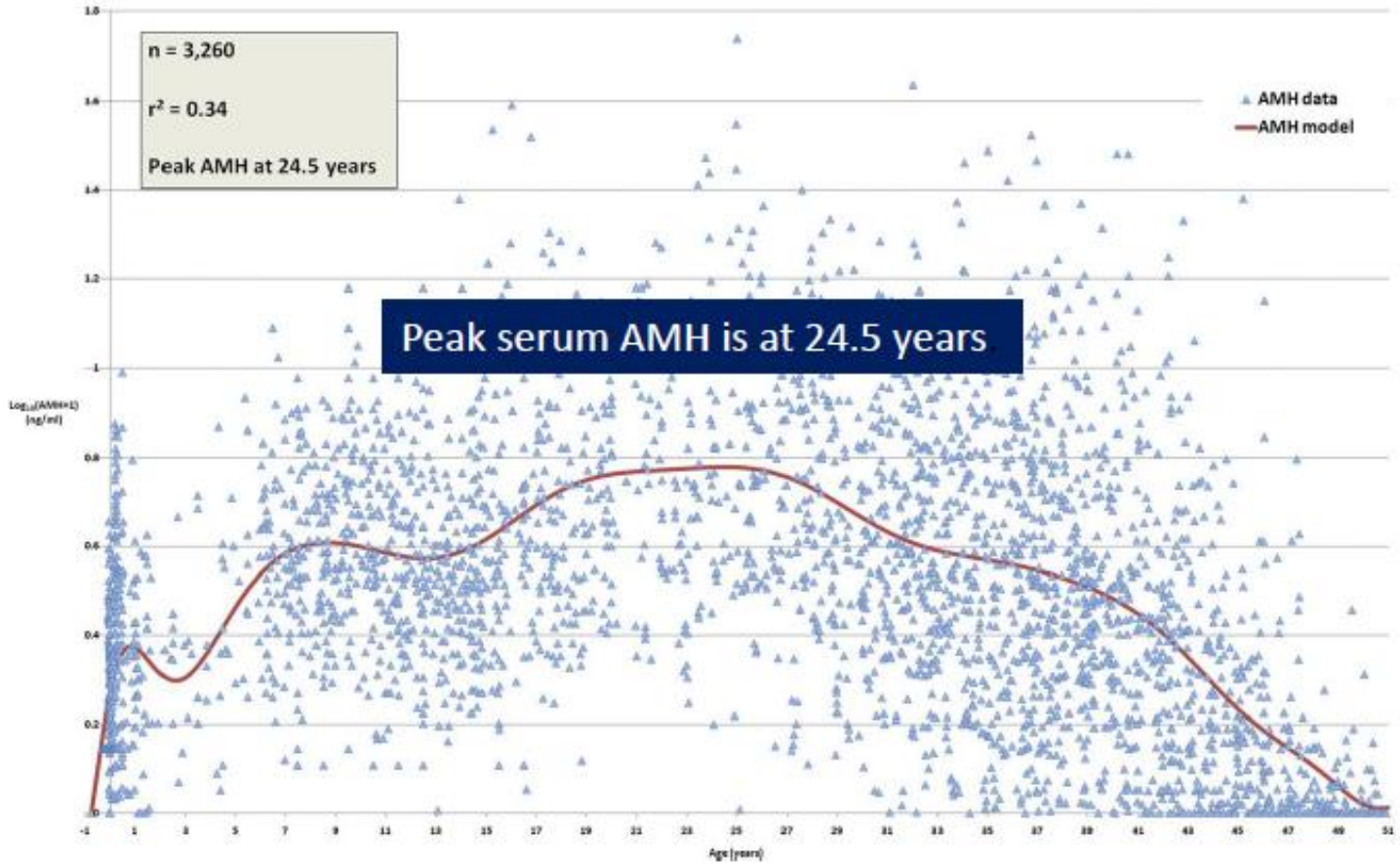




AMH variability throughout the menstrual cycle. Serum AMH appears to be stable

Hum Reprod Update, 2014:20(3):370–385

A validated model of serum antimullerian hormone (AMH) from conception to menopause.



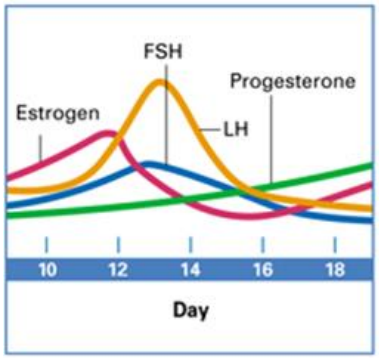
Fertil Steril 2013;99:1469–75

在生殖力評估未滿足的醫療需求
目前兩個方法的局限性

生物標記物

FSH and Estradiol

- 月經週期數值變化大
- 臨床上低靈敏度
- 不佳的臨床可靠性



AMH提供的價值

- 在月經週期的任何一天，都

  被測量
- 相比於AFC，AMH是有獨立測量值
- 對於可以預測不好的反應，以避免失望和成本

AMH – 新的黃金標準

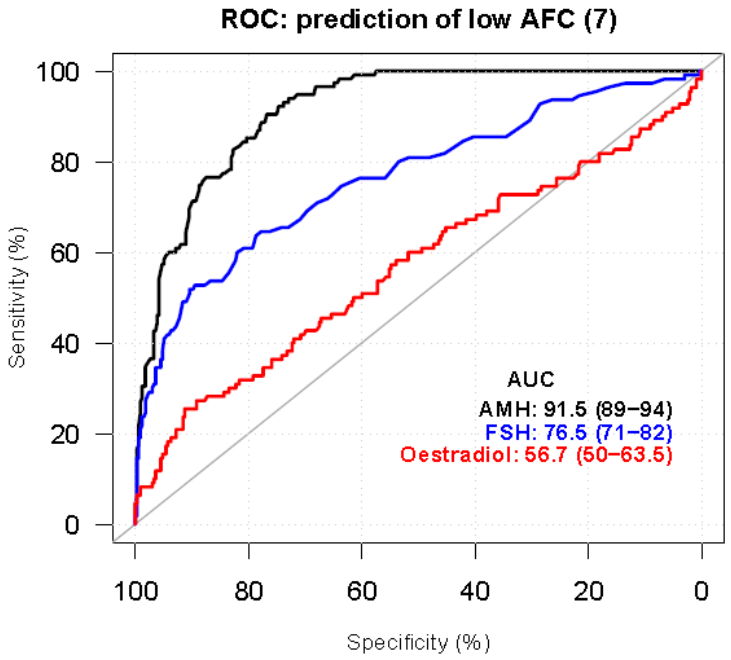
超音波

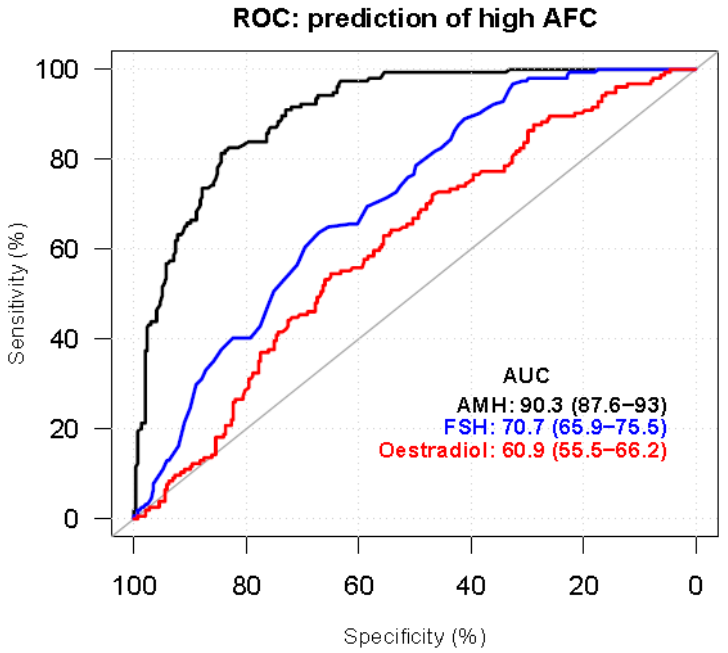
Antral Follicle Count

- 週期的變異
- 不同操作者的變異大

AMH優於目前的生物標記

相較於FSH 及E2，AMH 是一個最好預測AFC的生物標記





訊息

AMH 是一個最好預測AFC的生物標記

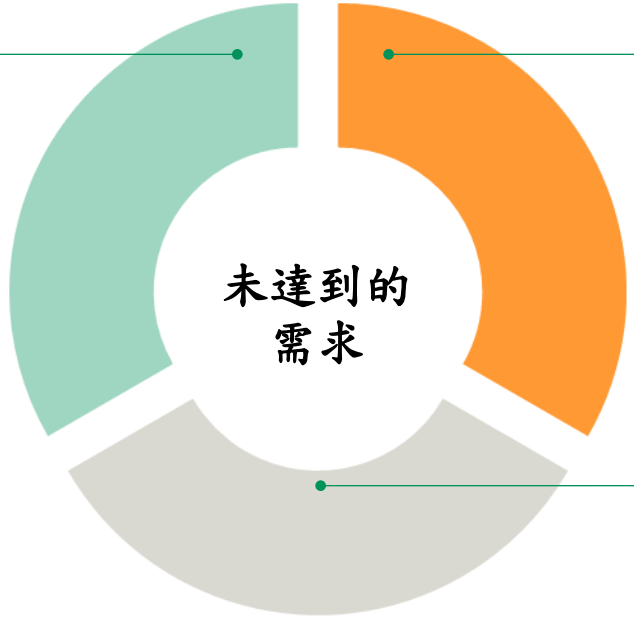
AMH 能夠在月經週期的每一天被測量

With courtesy of De Geyter C., University Women's Hospital, Basel, unpublished

AMH 檢測未達到的需求[1-3]

國際標準[1-3]

- To maximise the clinical utility of AMH measurement in IVF, there is a need to develop international standards endorsed by a relevant regulatory body
- Accepted standards would enable consistent interpretation of results across centres, permit lot-to-lot reliability to be assessed by manufacturers and allow assay performance to be evaluated over time



不同年齡層的參考值範圍[2]

自動化檢測[4]

1. Li HW et al. J Assist Reprod Genet 2012;29:1443–1446.
2. Nelson SM et al. Fertil Steril 2014;101:523–529.
3. Welsh P et al. Hum Reprod 2014;29:1035–1041.
4. Nelson SM. Fertil Steril 2013;99:963–969.

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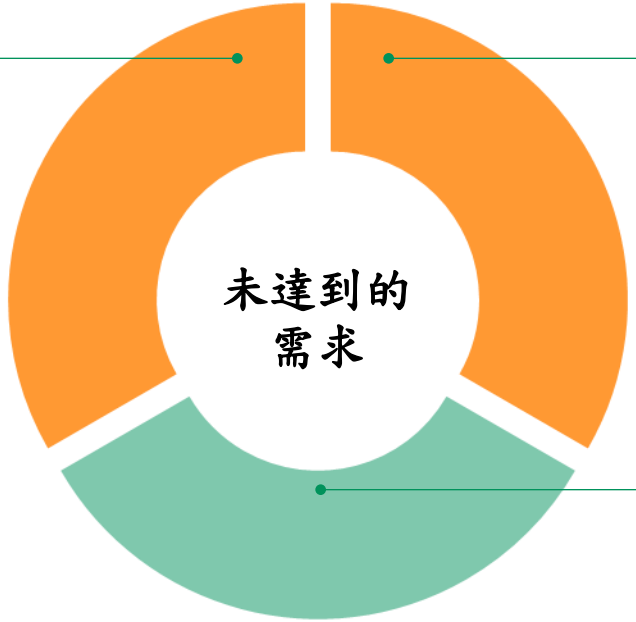

自動化檢測[4]

- Operator-dependent testing increases the risk of human error, which would be minimised by an automated assay
- An automated assay would save time and allow more efficient use of laboratory resources

1. Li HW et al. J Assist Reprod Genet 2012;29:1443–1446.
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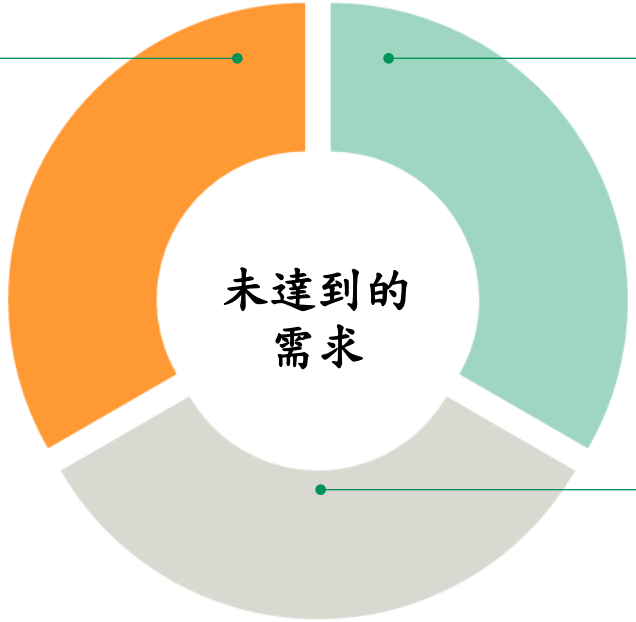

不同年齡層的參考值範圍[2]

- Validated age-specific ranges are required to interpret results effectively and would allow appropriate counselling to be offered of the basis of test results

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2. Nelson SM et al. Fertil Steril 2014;101:523–529.
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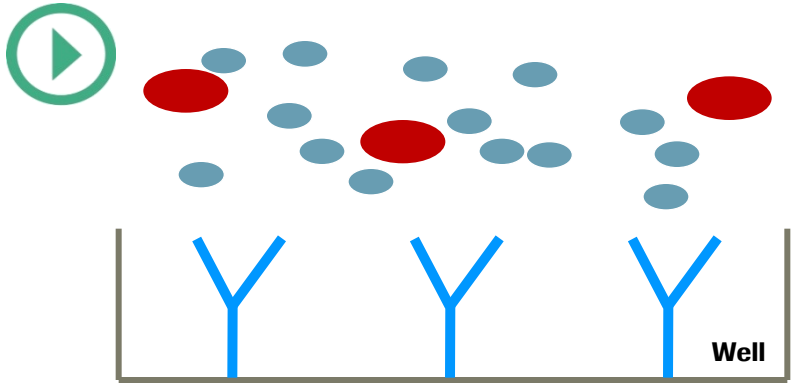
Elecsys® AMH沒有補體(Complement)的干擾

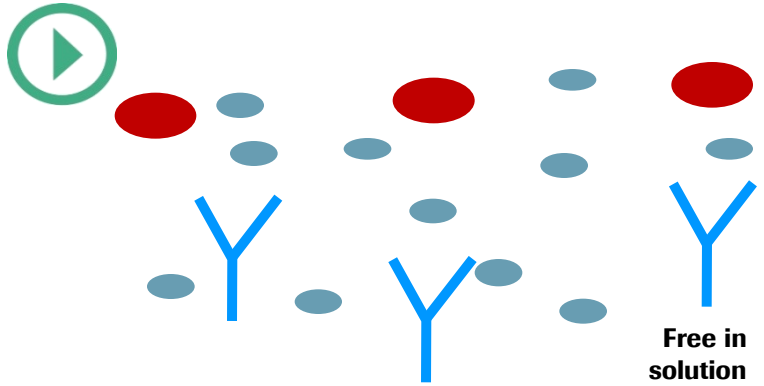
ELISA assays



Anti-AMH capturing antibodies (IgG)
Immobilized to the inside wall of each well of the ELISA plate[3]

- AMH values reported with an ELISA-based AMH assay have been lower than expected[1,2]
- This is potentially due to complement interference preventing the binding of AMH to assay antibodies[1,2]

Elecsys® AMH



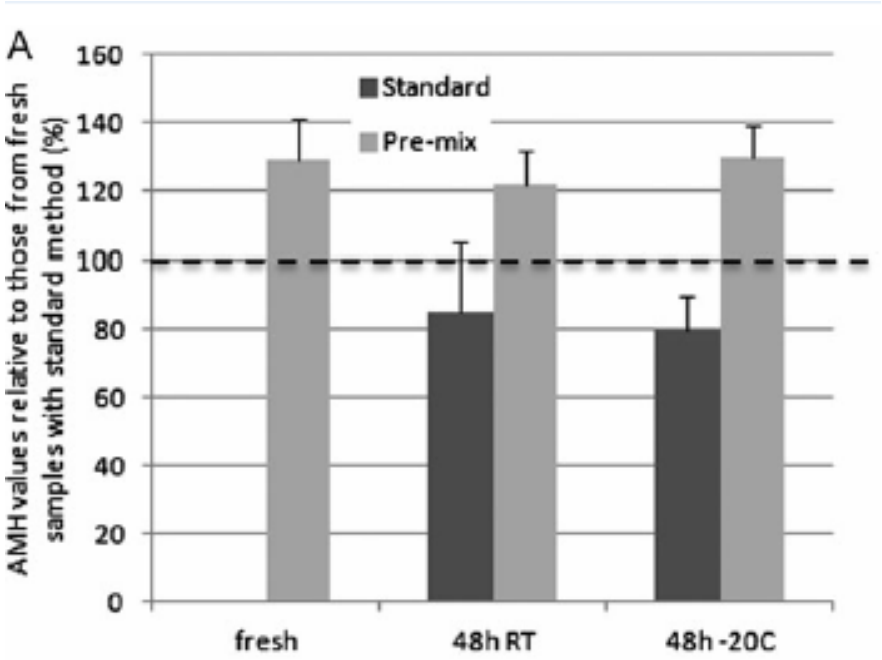
Free anti-AMH antibodies (IgG)
Free in solution

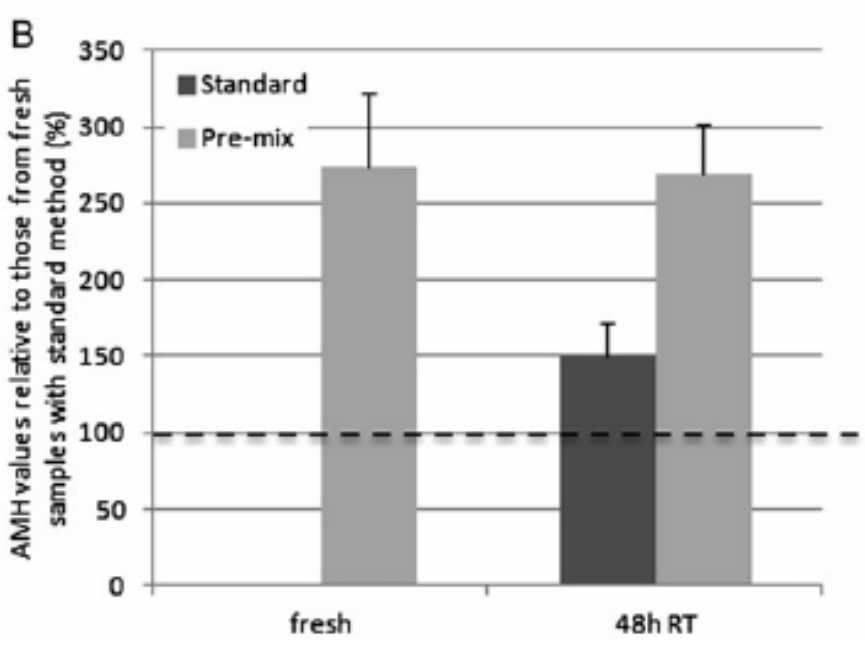
- The Elecsys® AMH assay uses the same antibodies as ELISA-based assays; however, no complement interference is observed[4]
- This is due to the unique assay format, which uses free IgG antibodies **in solution** that are not prone to complement binding[4]

AMH
Complement

1. Han X et al. Hum Reprod 2014;29:1042–1048.
2. Beckman Coulter. Urgent Field Safety Notice AMH Gen II ELISA (REF A79765).
3. Beckman Coulter. AMH Gen II ELISA package insert 2013.

對於懷孕及非懷孕婦女組群的血清AMH 結果





Han X et al. Hum Reprod 2014;29:1042–1048.

Two new automated, compared with two enzyme-linked immunosorbent, antimüllerian hormone assays

Scott M. Nelson, Ph.D.,[a] Ewa Pastuszek, M.S.,[b,c] Grzegorz Kloss, M.S.,[b] Iwona Malinowska, M.S.,[b] Joanna Liss, Ph.D.,[b] Aron Lukaszuk, B.S.,[b] Lukasz Plociennik, Ph.D.,[b] and Krzysztof Lukaszuk, M.D., Ph.D.[b,c,d]

[a] School of Medicine, University of Glasgow, Glasgow, United Kingdom; [b] NVICTA Fertility and Reproductive Center, Gdansk; [c] Department of Nursing, Medical University, Gdansk; and [d] INVICTA Fertility and Reproductive Center, Warsaw, Poland

Objective: To compare new automated antimüllerian hormone (AMH) assay performance characteristics from the new automated Elecsys AMH (Roche; Elecsys) and Access AMH (Beckman Coulter; Access) assays with the existing AMH Gen II ELISA (enzyme-linked immunosorbent assay; Gen II; Beckman Coulter) and AMH ELISA (Ansh Labs) assays.
Design: Prospective assay evaluation.
Setting: University-affiliated clinical chemistry laboratory.
Patient(s): Patients referred for serum AMH measurement (n = 83) before start of in vitro fertilization cycle between September 2014 and October 2014.
Intervention(s): None.
Main Outcome Measure(s): Serum AMH concentration.
Result(s): Intra-assay coefficients of variation were low; Ansh ≤ 9.0%; Gen II ≤ 5.8%; Access ≤ 10.7%; and Elecsys ≤ 2.8%. The Passing-Bablok regression equations (pmol/L) were y (Access) = 0.128 + (0.781 × Gen II); and y (Access) = 0.302 + (0.742 x Ansh). For y (Elecys) = 0.087 + (0.729 x Gen II) and y (Elecys) = 0.253 + (0.688 x Ansh Labs). For y (Elecys) = 0.943 − (0.037 × Access). For all the assays, AMH exhibited a moderate positive correlation with AFC (r = 0.62–0.64); number of cumulus oocyte complexes (r = 0.60–0.64); and metaphase II oocytes (r = 0.48–0.50). Accuracy of pregnancy prediction, as determined by area under the receiver operating characteristic curve, was uniformly low for all assays (0.62–0.63).

Fertility and Sterility, Volume 104, Issue 4, 2015, 1016–1021.e6

AMH不同年齡層的參考值範圍[1]

Table

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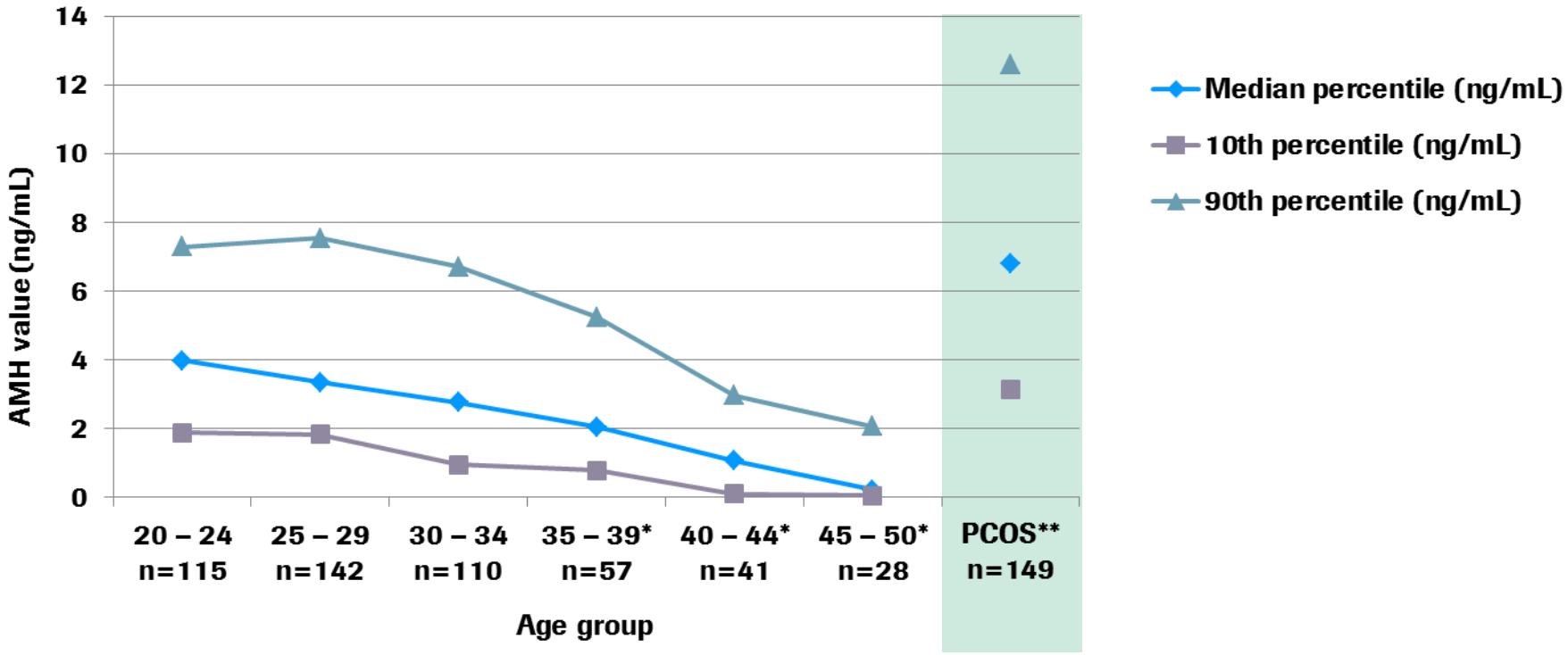

* Due to the lower numbers of patients in these age groups the extreme percentiles were not calculated[1]

** According to the revised diagnostic criteria of PCOS defined by the Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group[2]

- Obtained using the Elecsys® AMH assay in a study of a Caucasian population, with samples from 493 apparently healthy women and 149 women with PCOS (Roche study No. RD001727)
- Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges[1]

1. Anti-Müllerian Hormone. Elecsys and **cobas e** analyzers package insert 2014.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Hum Reprod 2004;19:41–47.

AMH不同年齡層的參考值範圍[1]

Graph

CLOSE

	N	5th perc. ng/mL	10th perc. ng/mL	Median perc. ng/mL	90th perc. ng/mL	95th perc. ng/mL
Healthy women (years)						
20 – 24	115	1.66	1.88	3.97	7.29	9.49
25 – 29	142	1.18	1.83	3.34	7.53	9.16
30 – 34	110	0.672	0.946	2.76	6.70	7.55
35 – 39	57*	-	0.777	2.05	5.24	-
40 – 44	41*	-	0.097	1.06	2.96	-
45 – 50	28*	-	0.046	0.223	2.06	-
PCOS women **						
	149	2.41	3.12	6.81	12.6	17.1

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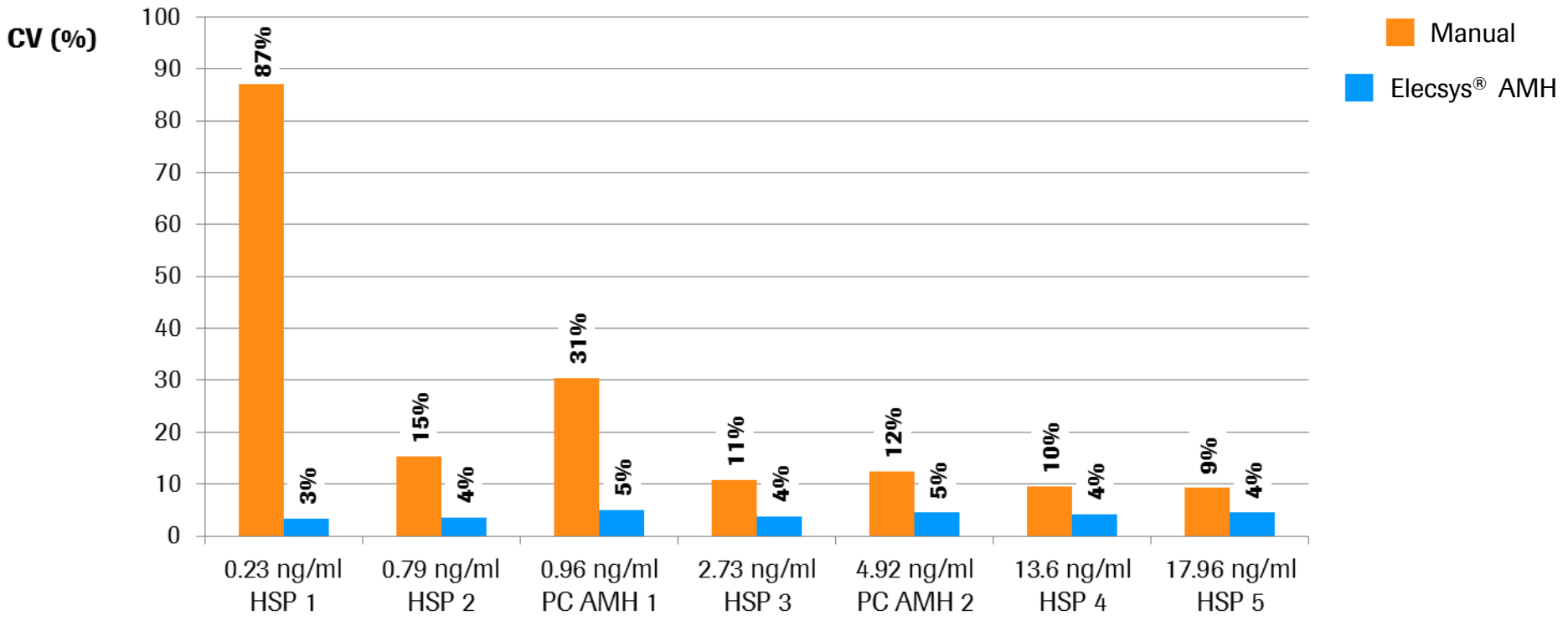
2. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Hum Reprod 2004;19(1):41–47.

Elecsys®AMH比常規手工方法具有更高的精密度



In a multicentre analysis* involving five different laboratories across Europe, the fully-automated Elecsys® AMH assay exhibited greater precision performance than the routinely used manual method[1]

* Run according to CLSI protocol (CLSI-EP5)

1. Schiettecatte J et al. Presented at IFCC WorldLab Congress, Istanbul, Turkey, 22–26 June 2014.

Roche Elecsys® 免疫項目

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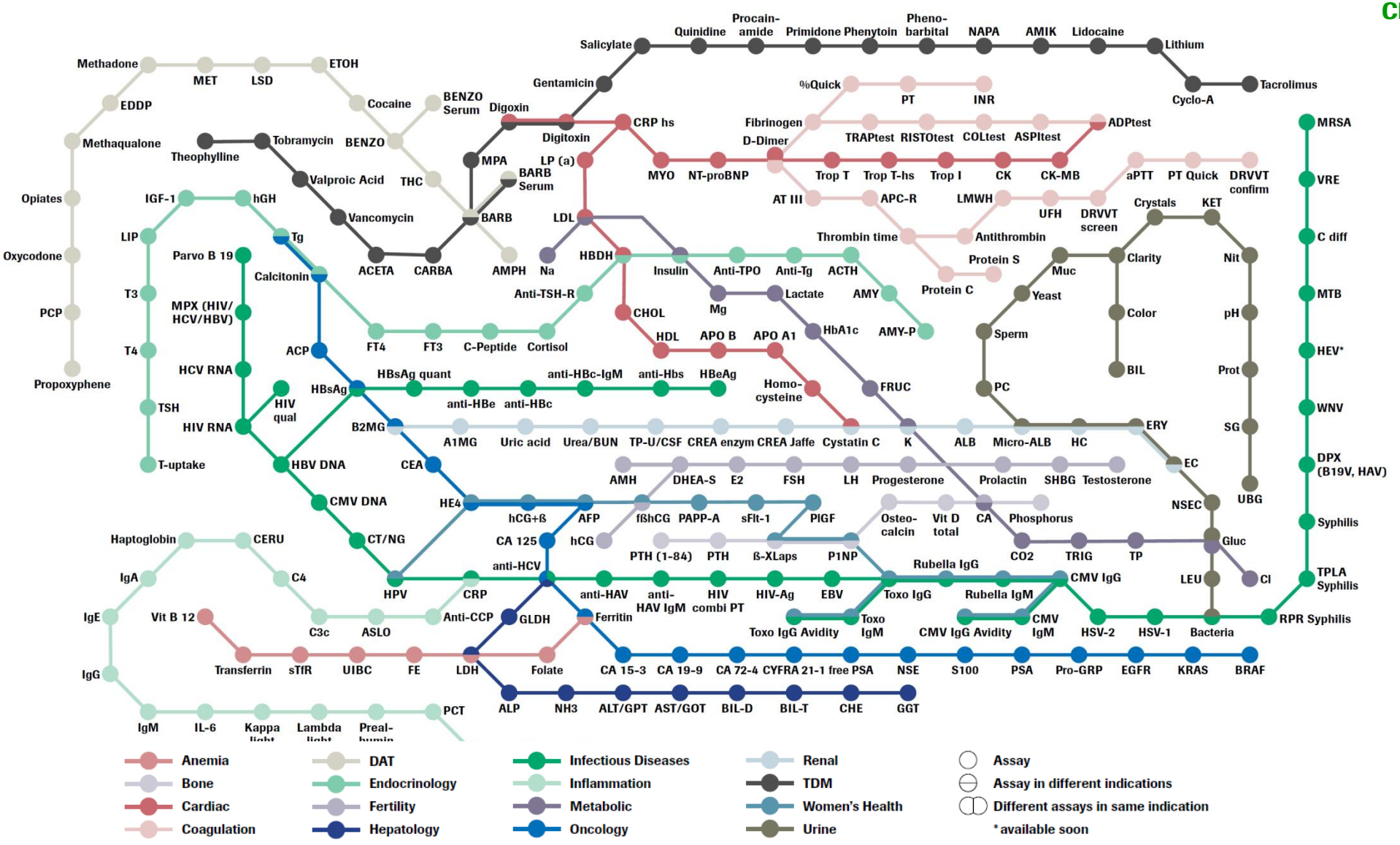

1. Roche Diagnostics test portfolio. Available at: http://www.cobas.com/home/indications/test-portfolio.html (Last accessed June 2014).

Thank you for your attention.

Roche Diagnostics Ltd.
6343 Rotkreuz
Switzerland