Fertility preservation after diagnosis of breast cancer

林口長庚 婦產部 生殖內分泌科
吳憲銘 醫師

Concept

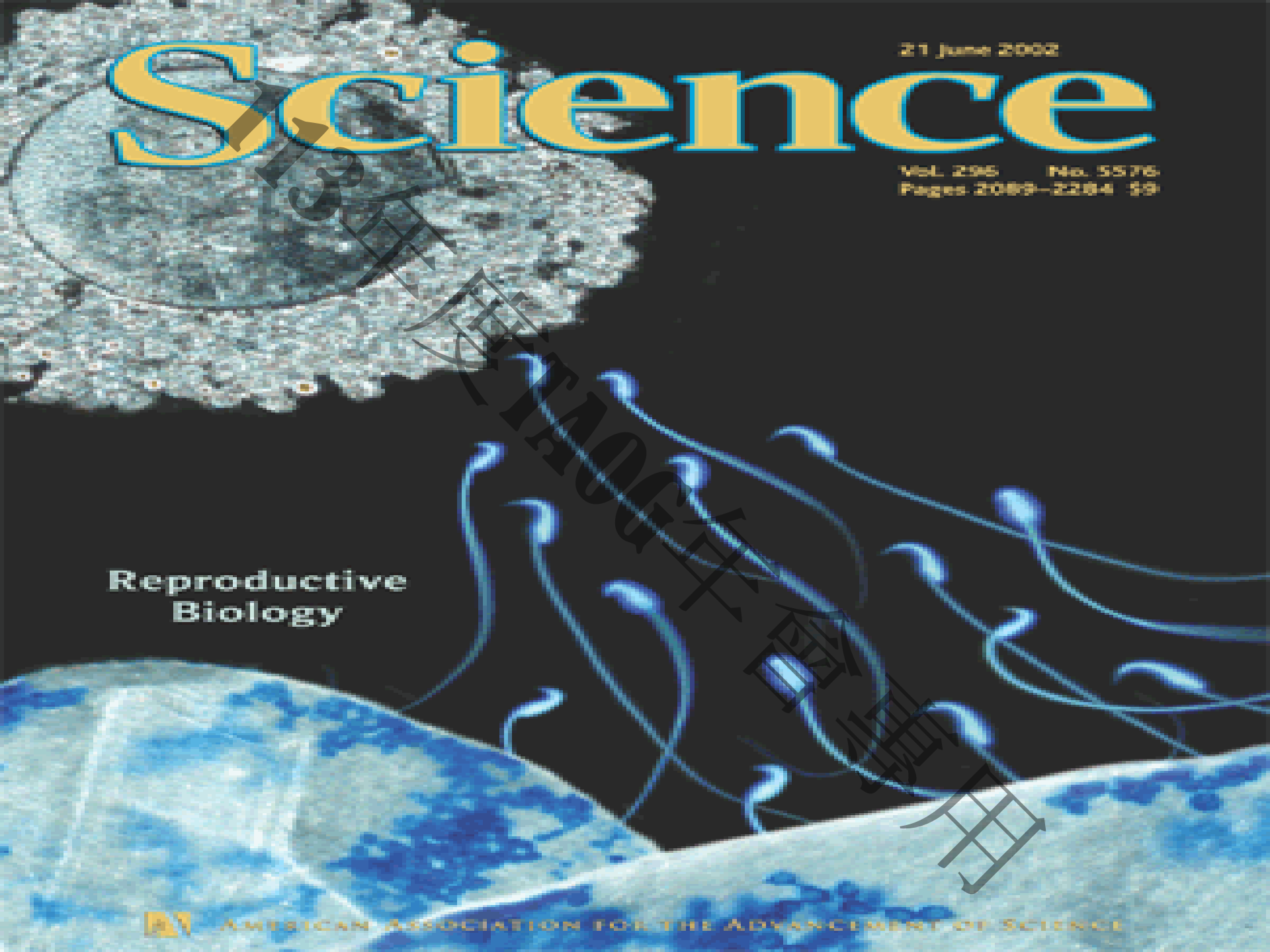
1. Background
2. When ?
3. How ?
4. Risky ?
5. Ethical issue
6. Suggestion


nature
The chicken genome
Cracking the code

21 June 2002

Science

Vol. 296 No. 5576
Pages 2089–2284 $9



Reproductive Biology

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

台灣生殖醫學會
Taiwanese Society for Reproductive Medicine

首頁 | 聯絡我們 | 入會申請 | 會員登入

關於學會 | 最新消息 | 學會會訊 | 學術活動 | 生殖機構 | 會員專區 | 相關連結 | 民眾專區 | 境外醫療

首頁 > 最新消息

最新消息

2021/08/13 癌症病人生育能力保護共識宣言

生育保護通則共識宣言_2021年版.pdf

附檔由財團法人癌症希望基金會提供 (經台灣生殖醫學會審閱)
For questions please contact:
02-3322-6287
www.ecancer.org.tw

Fertility preservation strategies

If the treatment includes:	The following options should be considered:
Oncologic surgery	Fertility-sparing surgery preserving gonads. Preservation of the uterus in females. Use of cryopreservation may also be considered prior to surgery if the risk of gonadal damage is high
Radiation therapy to pelvic organs and gonads	Shielding aiming at reducing damage of reproductive organs and surgical ovarian transposition Use of cryopreservation may also be considered prior to radiotherapy
Cytotoxic treatment with high risk of gonadal damage	Use of cryopreservation methods such as sperm banking for males, freezing of embryos and oocytes for females and gonadal tissue freezing
Hormone therapy for estrogen-sensitive breast cancer	Cryopreservation may be considered in women >33 years of age when being planned for a 5-year tamoxifen treatment and >28 years if a 10-year treatment is planned, as natural fertility diminishes with age.

Int. J. Mol. Sci. 2019, 20, 4720
Front Endocrinol . 2022 Oct 24;13:985525
Gynecol Endocrinol. 2022 Nov 20;1-6.
BMC Womens Health. 2022 Nov 7;22(1):436

Stages of follicular development

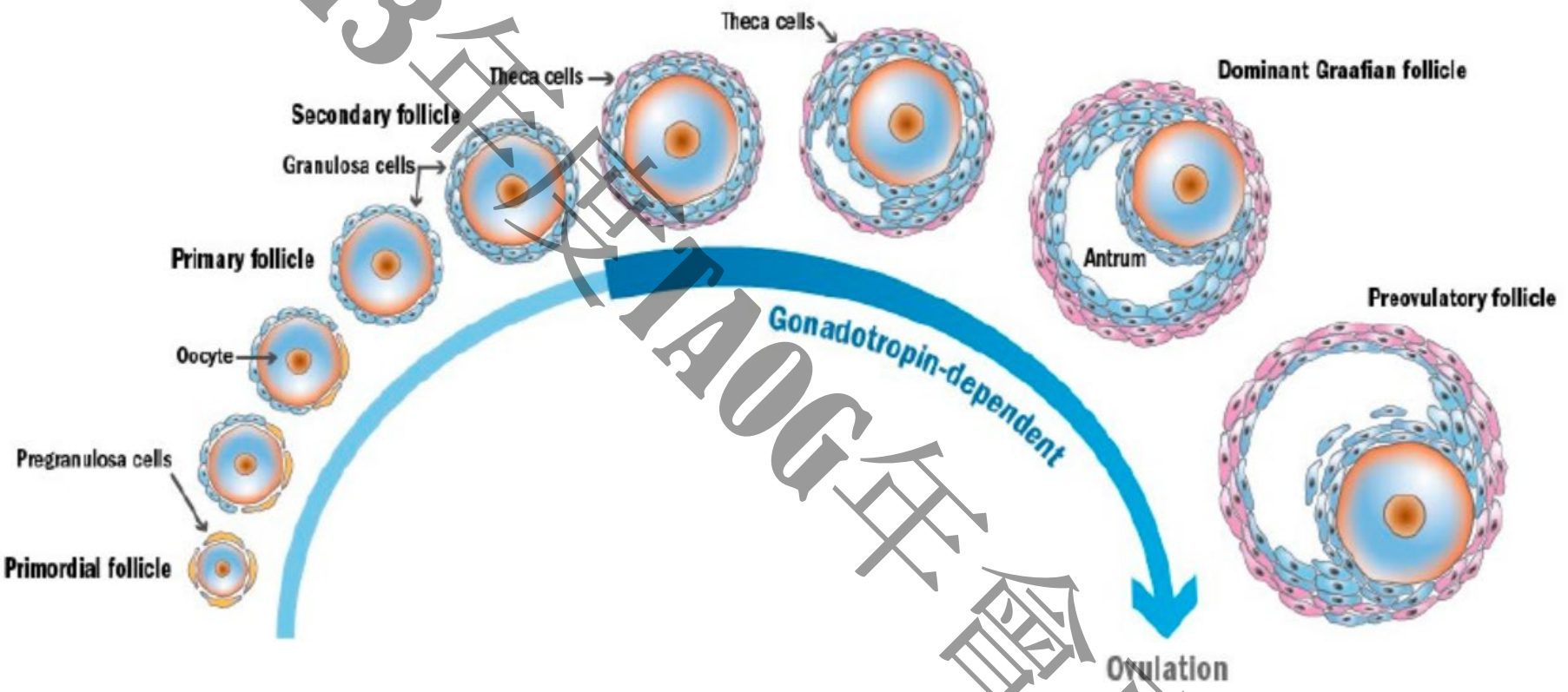
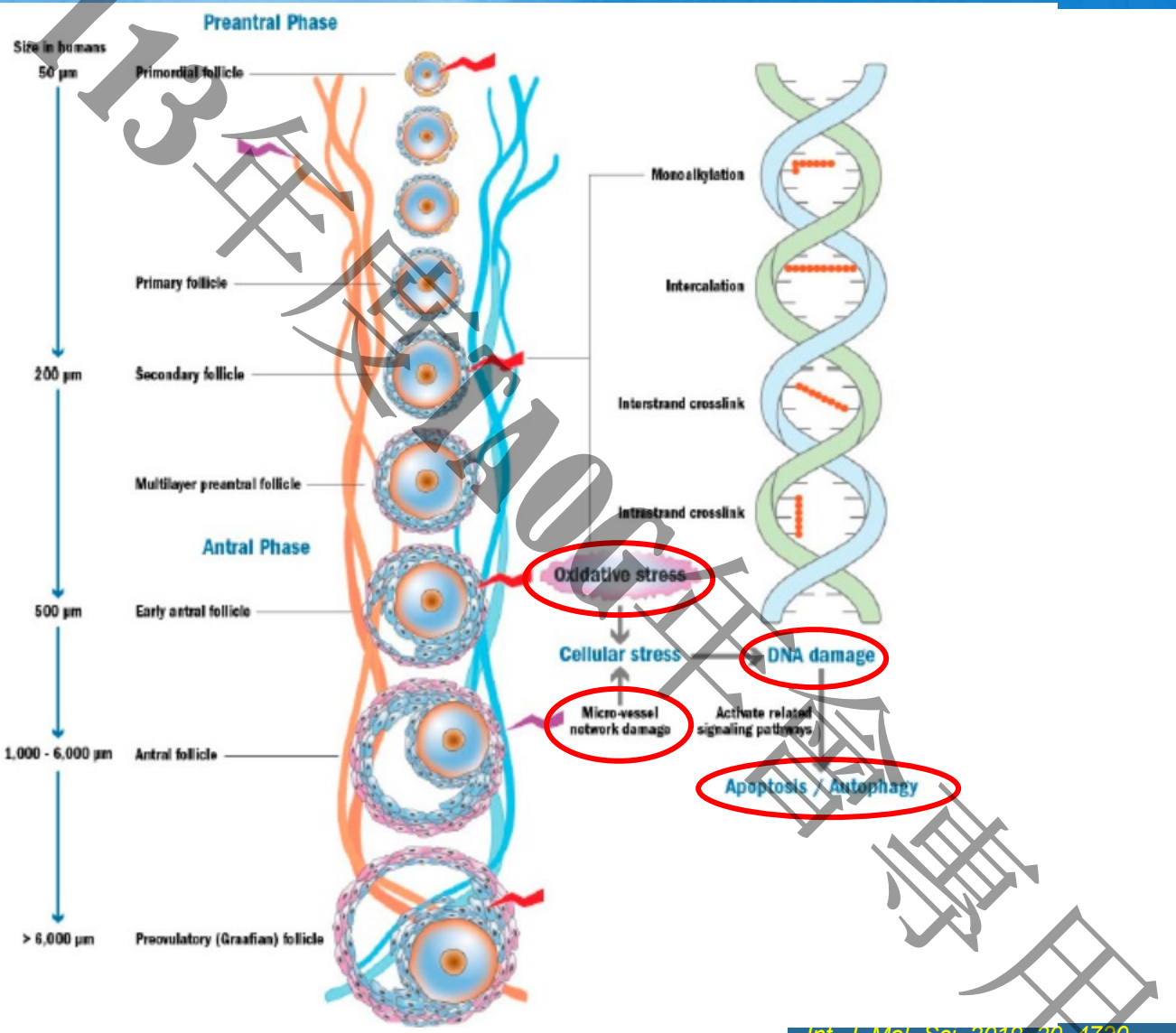


Figure 2. Different stages of follicular development

Int. J. Mol. Sci. 2019, 20, 4720
Front Endocrinol . 2022 Oct 24;13:985525
Gynecol Endocrinol. 2022 Nov 20;1-6.
BMC Womens Health. 2022 Nov 7;22(1):436

Proposed mechanisms of chemotherapy-induced ovarian damage



Int. J. Mol. Sci. 2019, 20, 4720
Front Endocrinol . 2022 Oct 24;13:985525
Gynecol Endocrinol. 2022 Nov 20;1-6.
BMC Womens Health. 2022 Nov 7;22(1):436

Concept

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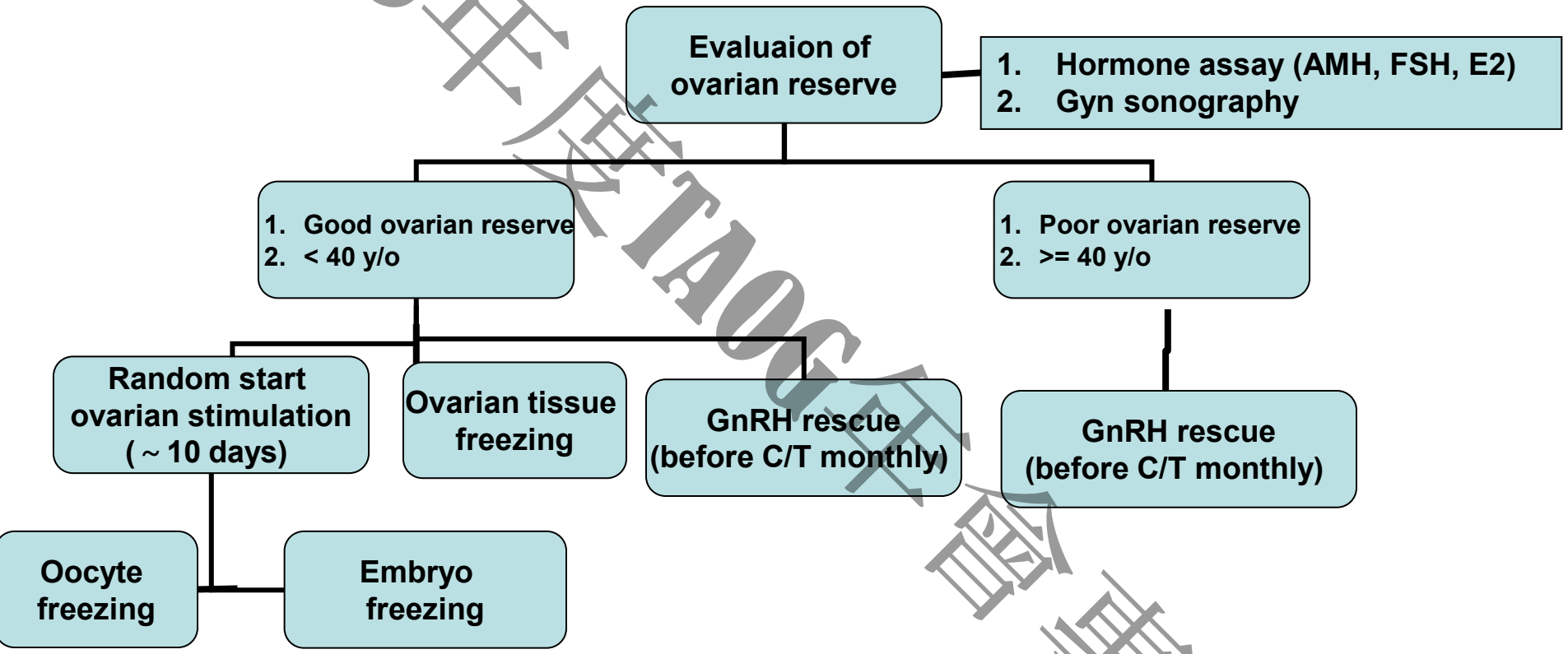
Fertility preservation tree



NEJM 2009 ;360:902

F&S 2013 ;100:1214

J Clin Oncol. 2015 Aug 1; 33(22): 2424–2429

Front Neuroendocrinol. 2021 Jan;60:100876.

Concept

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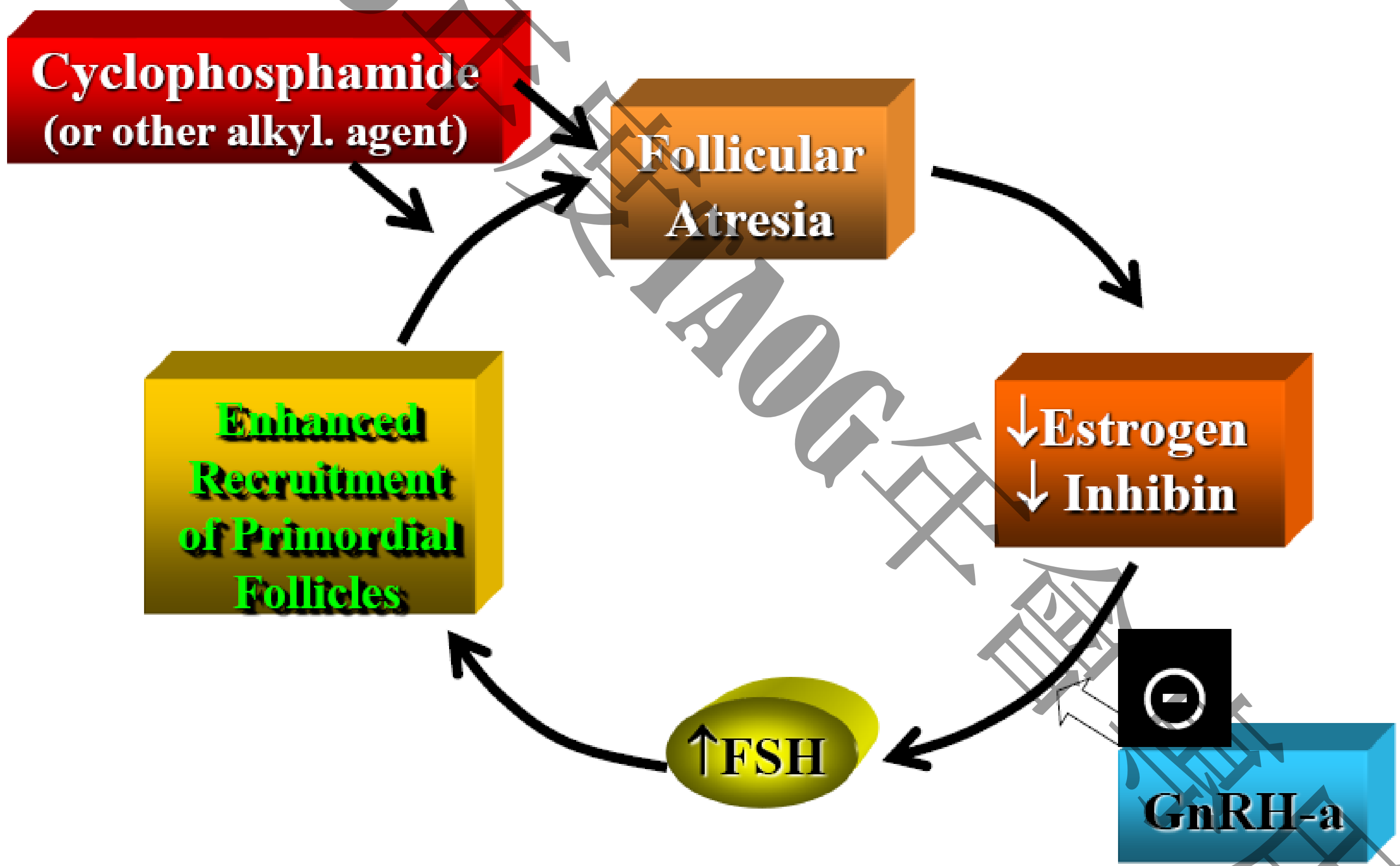
Mechanism of GnRH rescue effect



Hum Reprod Update 2008;14:553-561

Front Neuroendocrinol. 2021 Jan;60:100876.

Cryopreservation techniques


The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

Fertility Preservation in Women

Jacques Donnez, M.D., Ph.D., and Marie-Madeleine Dolmans, M.D., Ph.D.

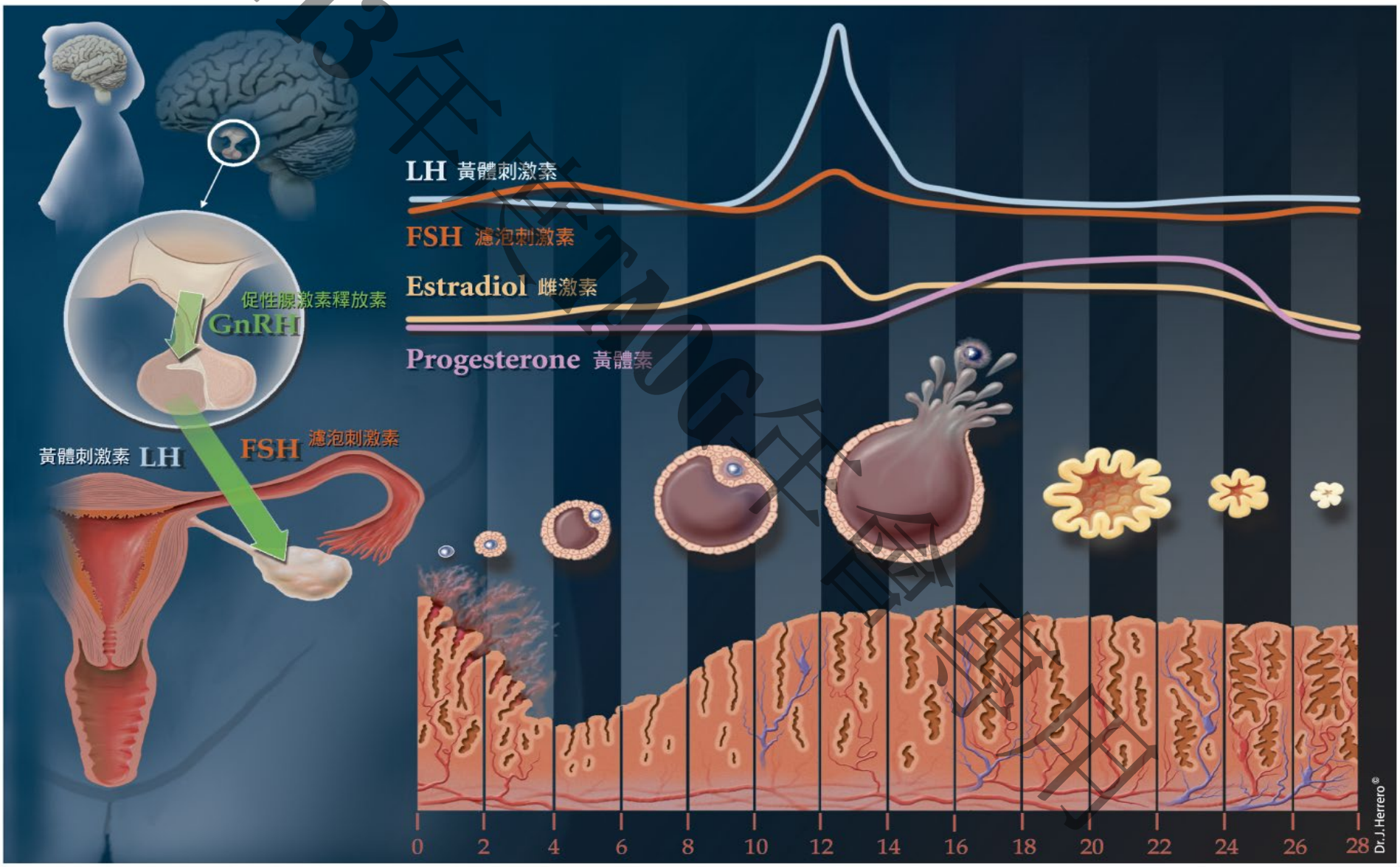
Embryo	• Requires a male partner
Oocyte	• Benign indications or personal reasons • Reproductive autonomy
Ovarian tissue	• 2020, ASRM **removes the experimental label** from Ovarian Tissue Cryopreservation (OTC): pediatric research must continue • For patients who need immediate chemotherapy

Oocyte or embryo cryopreservation

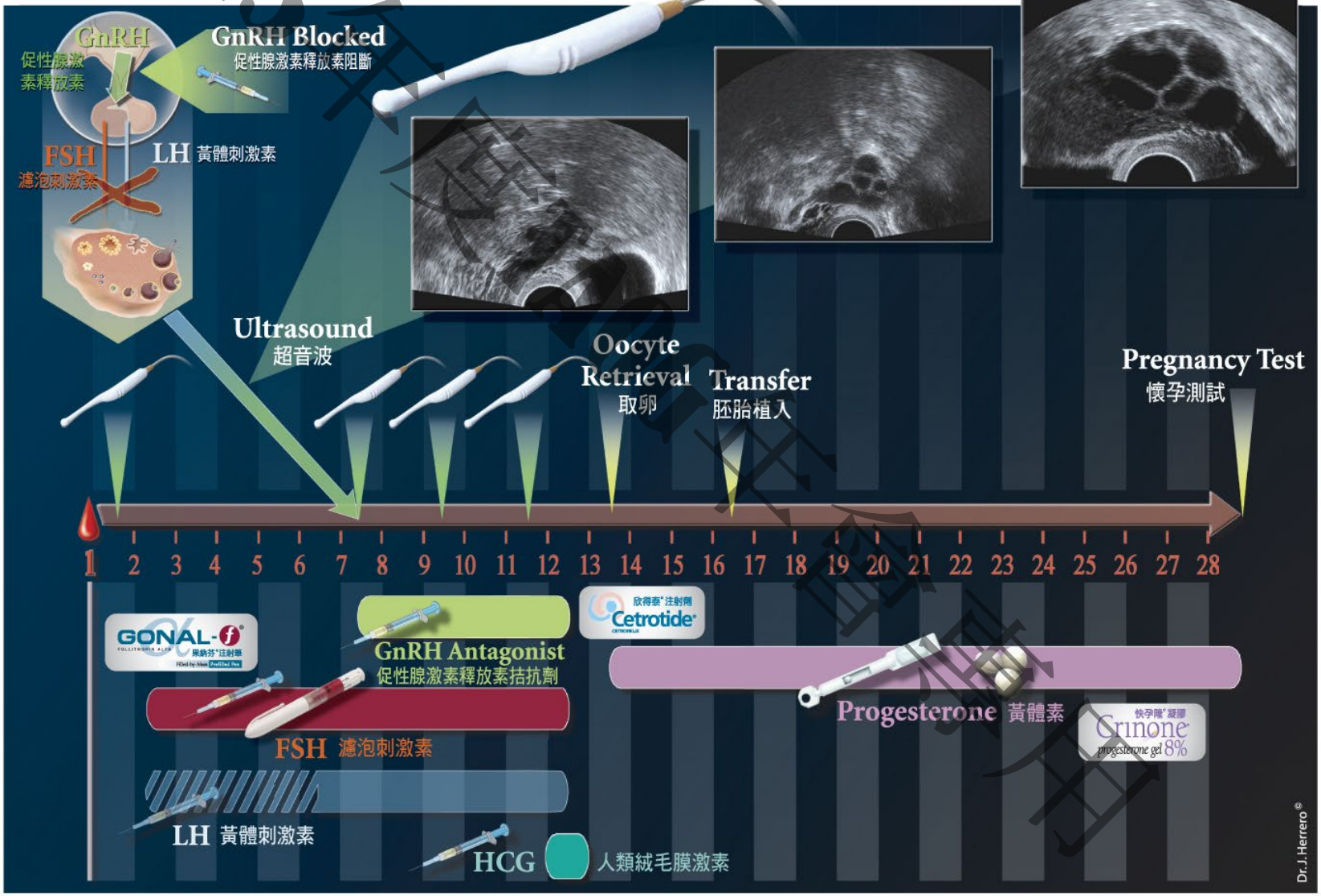
First IVF baby

Louise Brown, the first in vitro fertilization (IVF) baby, was born on July 28, 1978.

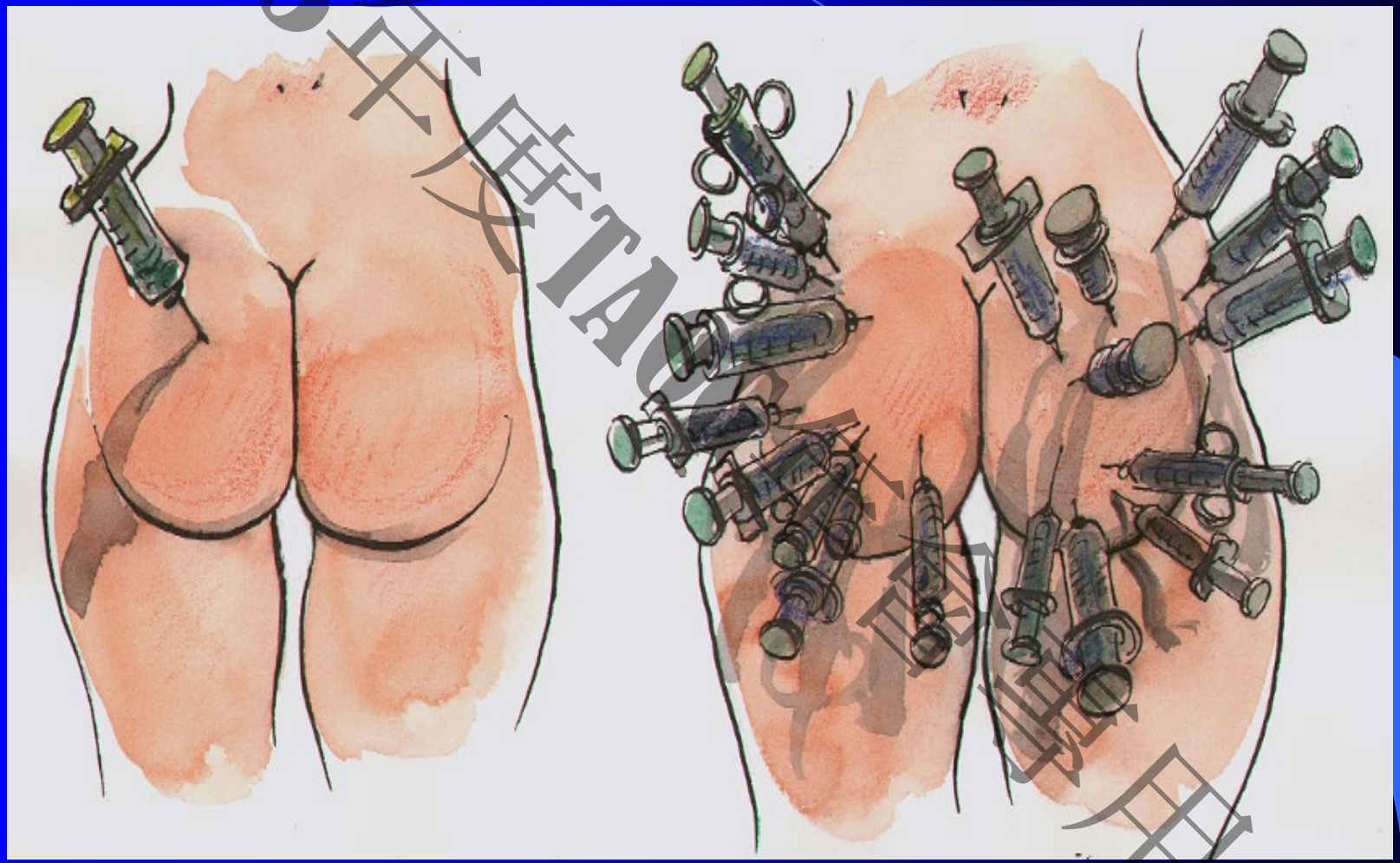
Menstrual cycle



Ovarian Stimulation; GnRH Antagonist Protocol
促性腺激素釋放素拮抗劑方案

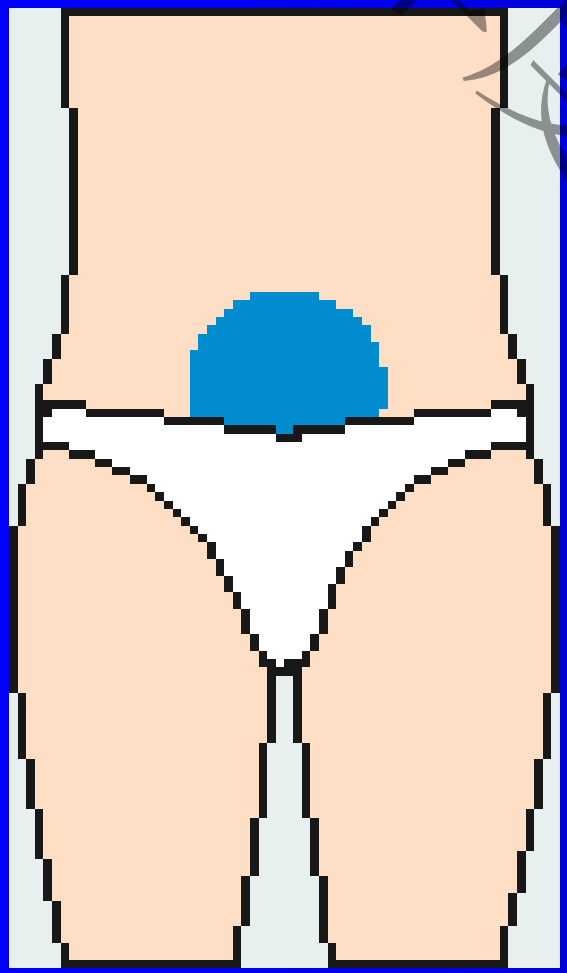


排卵針

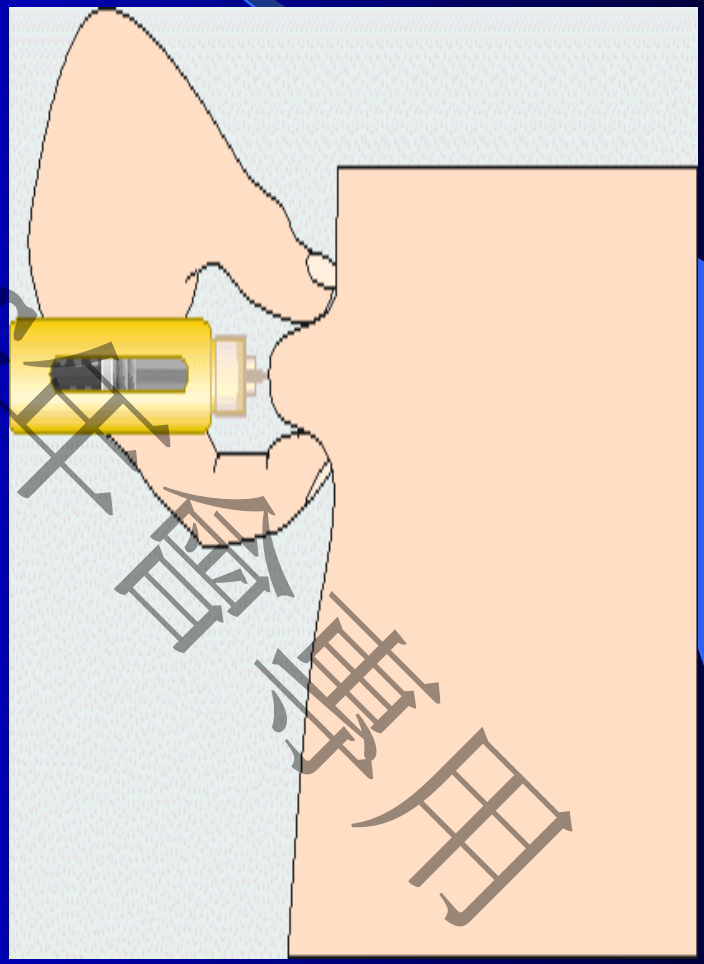


Self-injection

Injection site; abdomen



Needle insertion; 90 °C



Random start

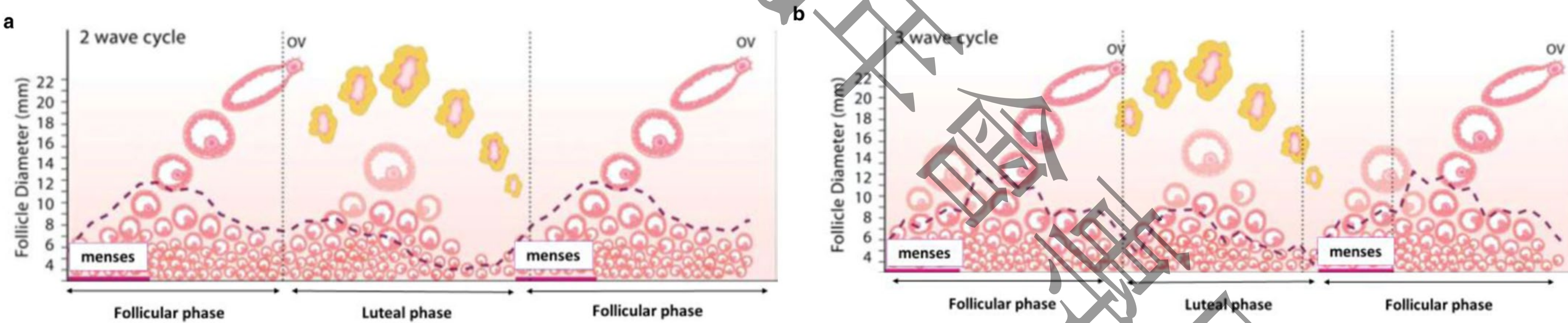
RBMO

ELSEVIER

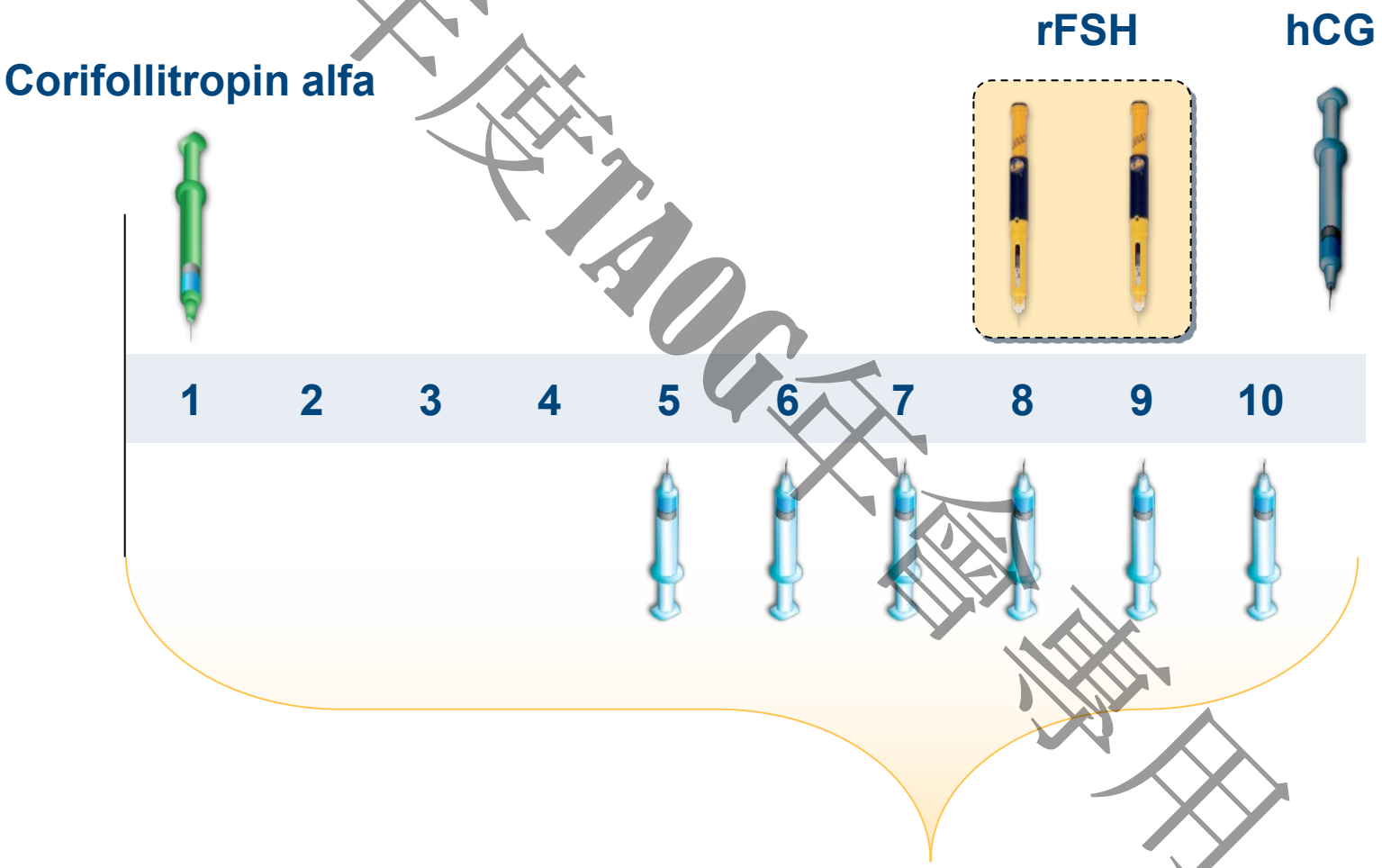
REVIEW

CrossMark

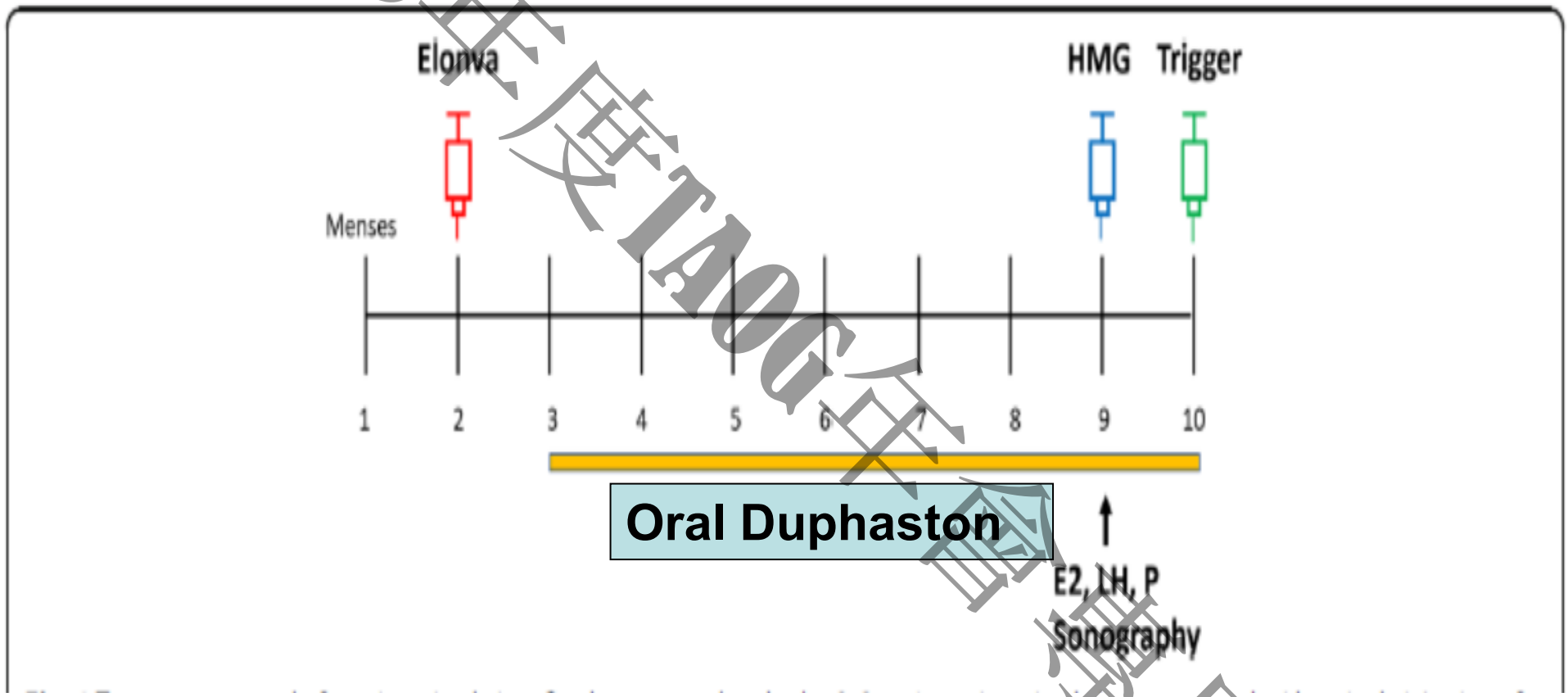
New strategies of ovarian stimulation based on the concept of ovarian follicular waves: From conventional to random and double stimulation



個人化打針療程

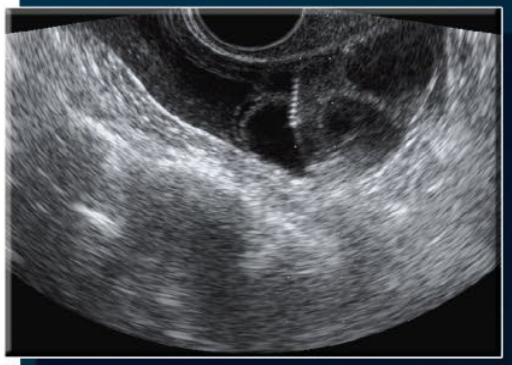


個人化打針療程

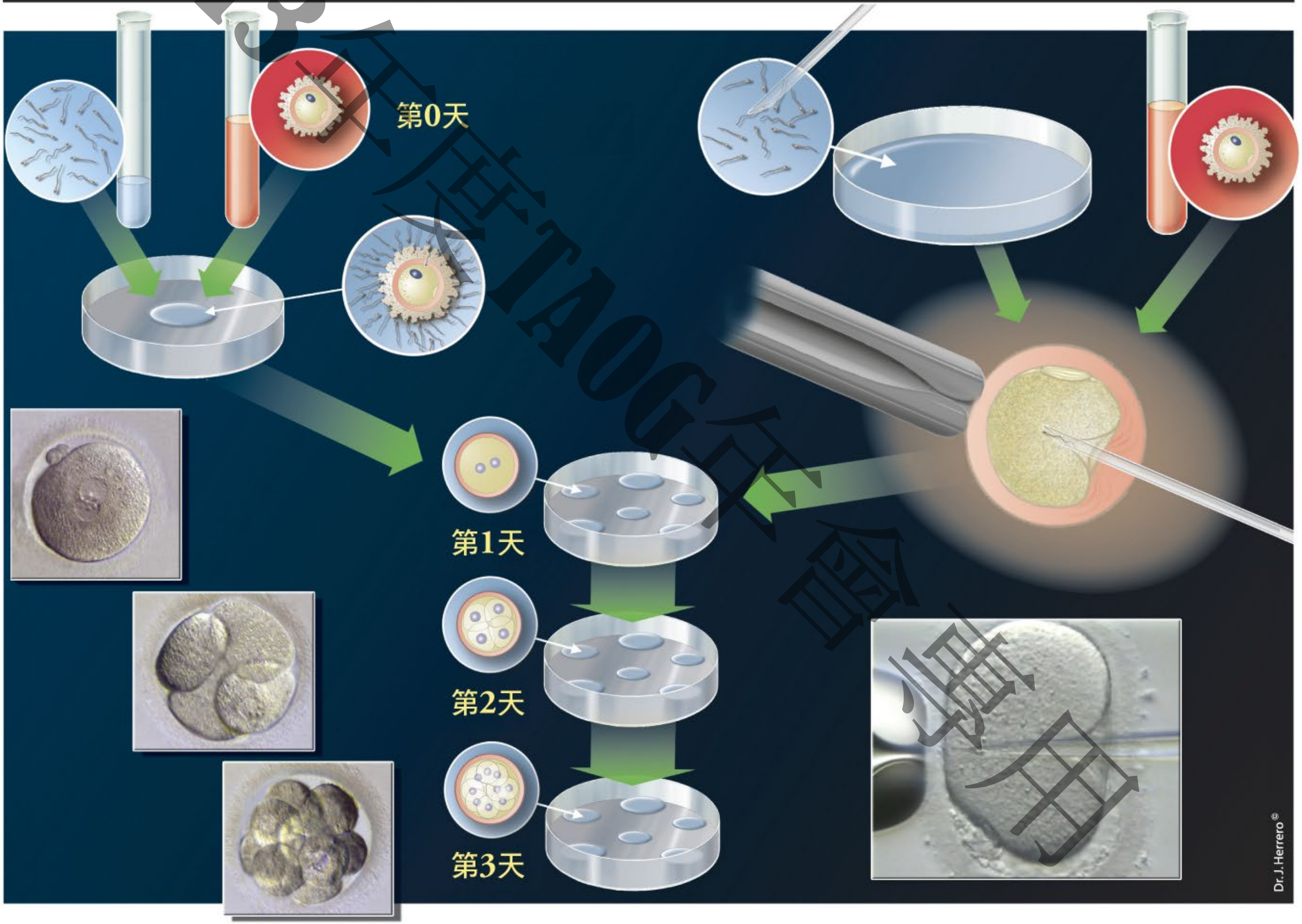


Huang and Li. Reproductive Biology and Endocrinology (2018) 16:18.

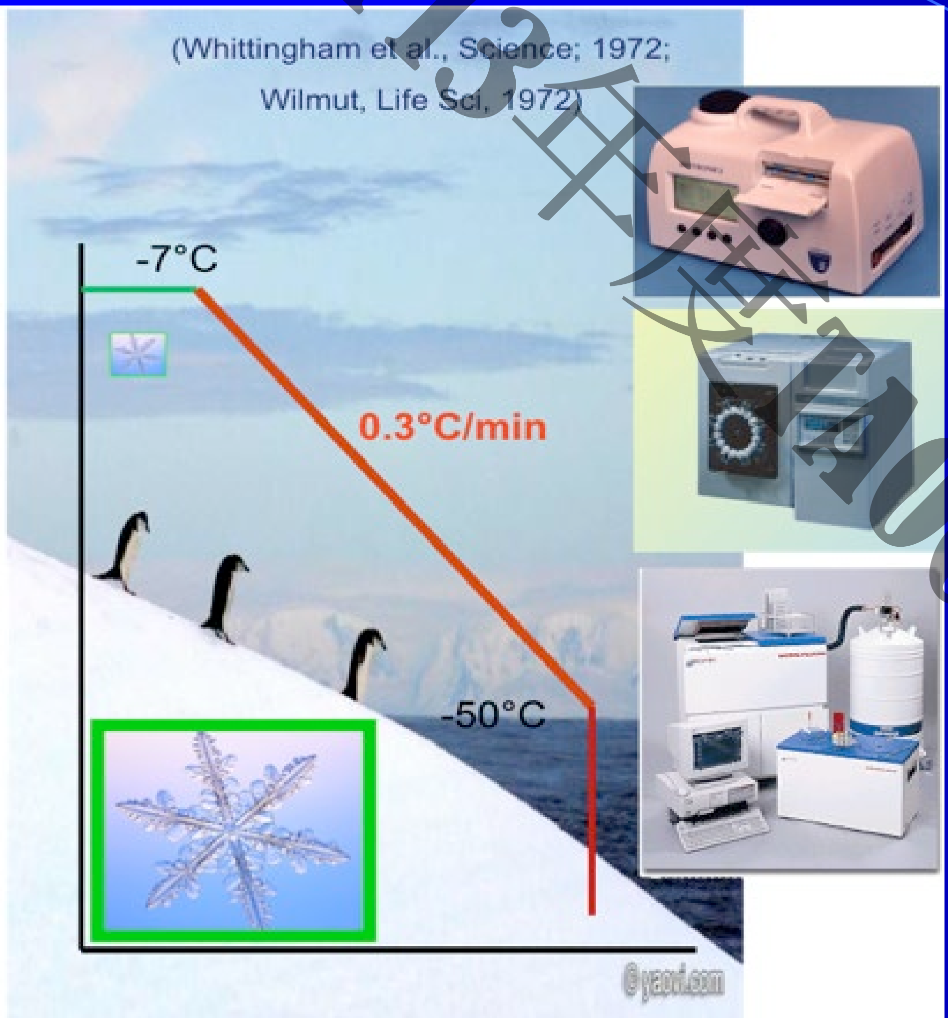
Oocyte Retrieval
取卵



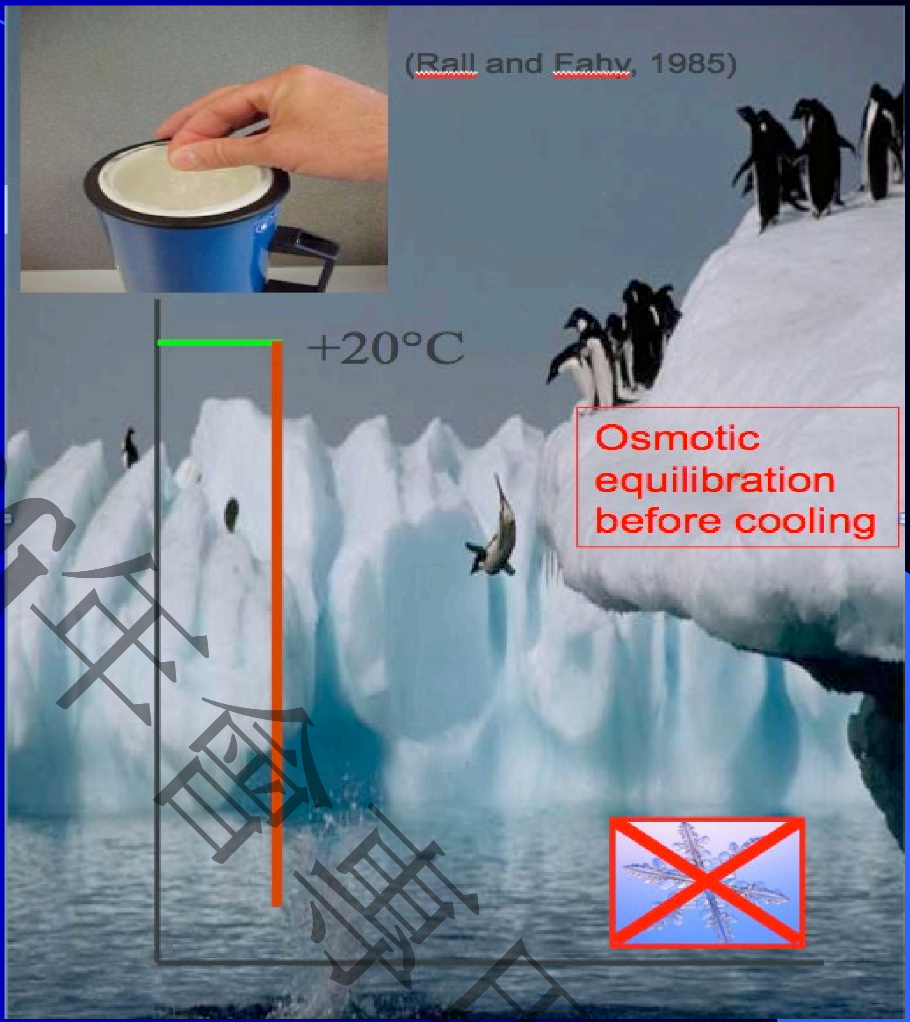
Fertilisation; Invitro Fertilisation (IVF) and Intracytoplasmic Sperm Injection (ICSI) 授精；體外授精及卵細胞質內單精蟲注射



Gamete and embryo cryopreservation



Slow freezing



Vitrification

Kuwayama et al. RBM Online 2005;11:300.
Chen et al. Taiwan J Obstet Gynecol 2009;48:15.
Tarlatziz et al. Curr Opin Obstet Gynecol 2009;21:270.

- In 2012 the American Society for Reproductive Medicine removed the "experimental" label from the procedure, citing studies about improved success rates and data that showed no increase in birth defects in babies.

美國生殖醫學會觀點

- NYU's clinic now performs 5 to 10 egg freezing retrievals a week. "Five years ago, only 5 percent of our procedures were egg freezing, and that was mostly for cancer patients. **In 2013 egg freezing accounted for a third of our business**, and the vast majority were elective.

Egg-freezing should be available to all UK women, experts urge

Specialists say fertility techniques that have enabled women with cancer to store eggs should be more widely accessible

Sarah Boseley, health editor
The Guardian, Friday 3 October 2014

Jump to comments (31)

In the UK, only 20 babies have yet been born from frozen eggs, according to the Human Fertilisation and Embryology Authority. Photograph: Alamy/Alamy

歐洲生殖醫學會觀點

Prior to December 2012, around 18,000 eggs had been stored in the UK for patients' own use, the HFEA said. Around 580 babies have been created from frozen eggs and there have been 20 live births.

Screen Shot 2014-12-16 at 下午 10.51.18.png

最新消息

2018/02/02 **台灣生殖醫學會冷凍卵子指引 2018**

台灣生殖醫學會冷凍卵子指引2018

1. 主旨：

凍卵是指因為疾病，醫療或是其他因素不適合短期內懷孕，或是可預期會因為治療或是疾病的進程可能導致卵巢功能提早衰退(醫療性凍卵)，有些不適合在短期間內有懷孕計畫的女性，希望先保存卵子，以留住日後生育機會的一項技術(個人預防性凍卵)。

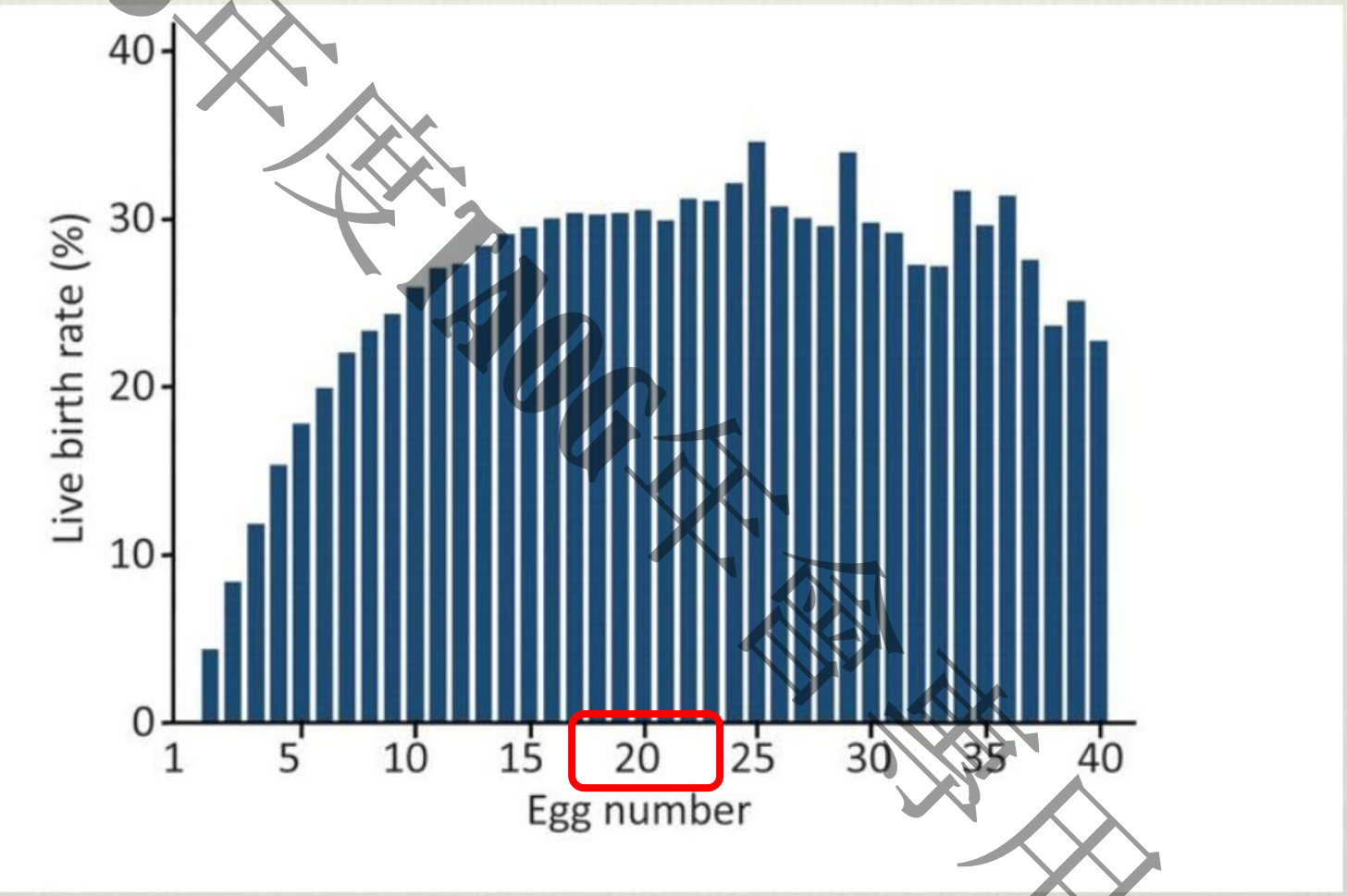
1. 背景說明：

過去凍卵的對象主要是年輕罹癌的女性，因為要接受化療、放射線治療而擔心影響卵子數量與品質，甚至卵巢衰竭，或是因治療需延後生育時程，擔心年齡增長使受孕機會降低，因此先行凍卵，待日後治癒再解凍卵子使用。在2012年美國生殖醫

台灣生殖醫學會冷凍卵子指引 2018

- 卵子冷凍不再是實驗階段，可進入臨床應用。
- 未婚女性可用於保存生育能力，目前已有成功個案數例，但仍須更多資料佐證其效果。
- 冷凍卵子在年輕女性和新鮮卵子有相近的懷孕率，年紀較大者效果則仍不清楚，需要更多資料證實。
- 目前在有限的資料顯示下沒有增加胎兒異常的機率，但仍需更多的資料來證實。
- 35歲以下建議接受1至3個取卵週期， 35歲以上則可能需要更多次，以保存15-20個卵子為原則。

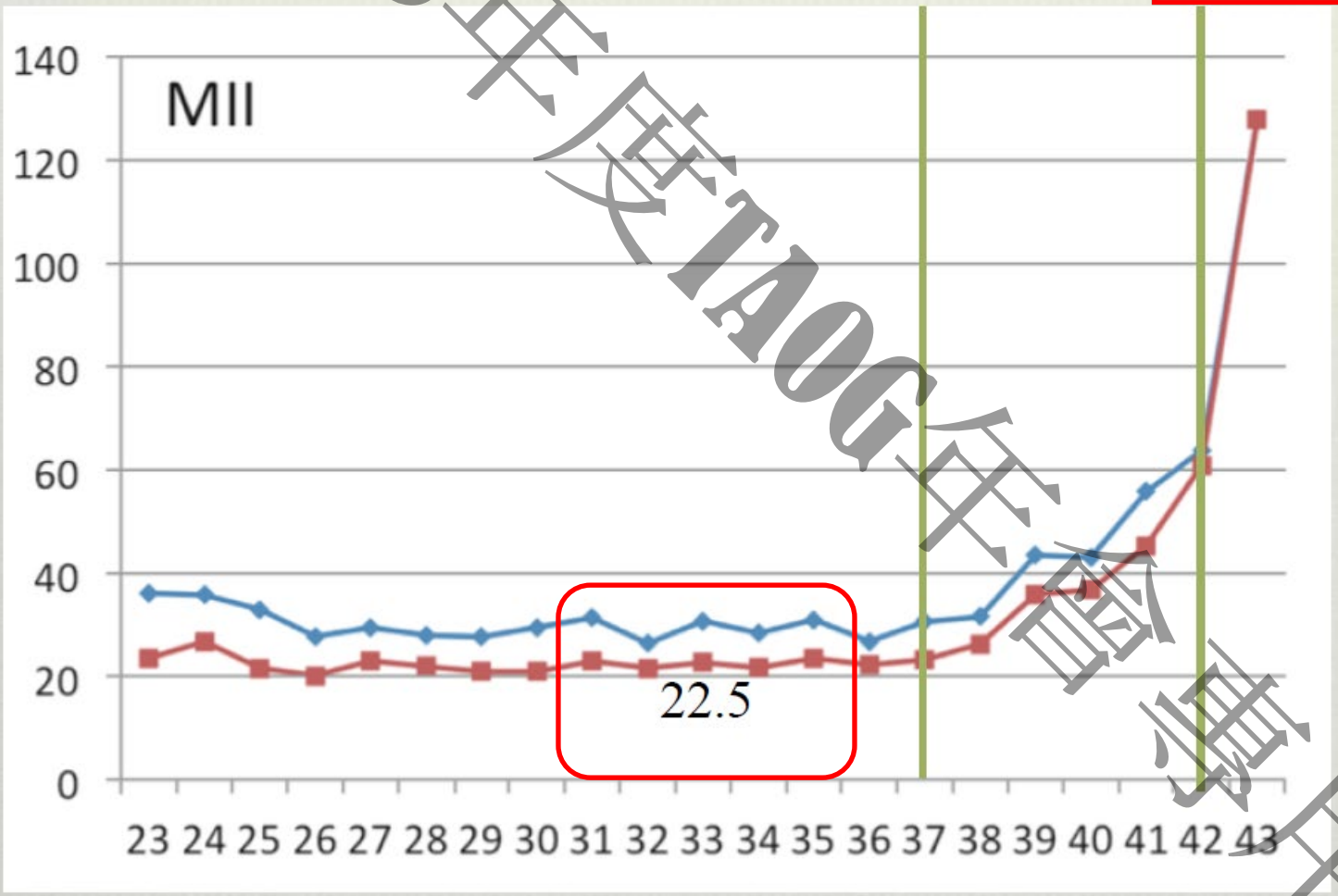
(How to determine cycles or oocytes for individual patient)



Sakkara et al. Hum. Reprod. 2011;26:1768-1774

The mean number of mature oocytes needed per live birth in the age group from 23 up to 37 years is 22.5 (SD: 1.55)

歐洲生殖醫學會觀點

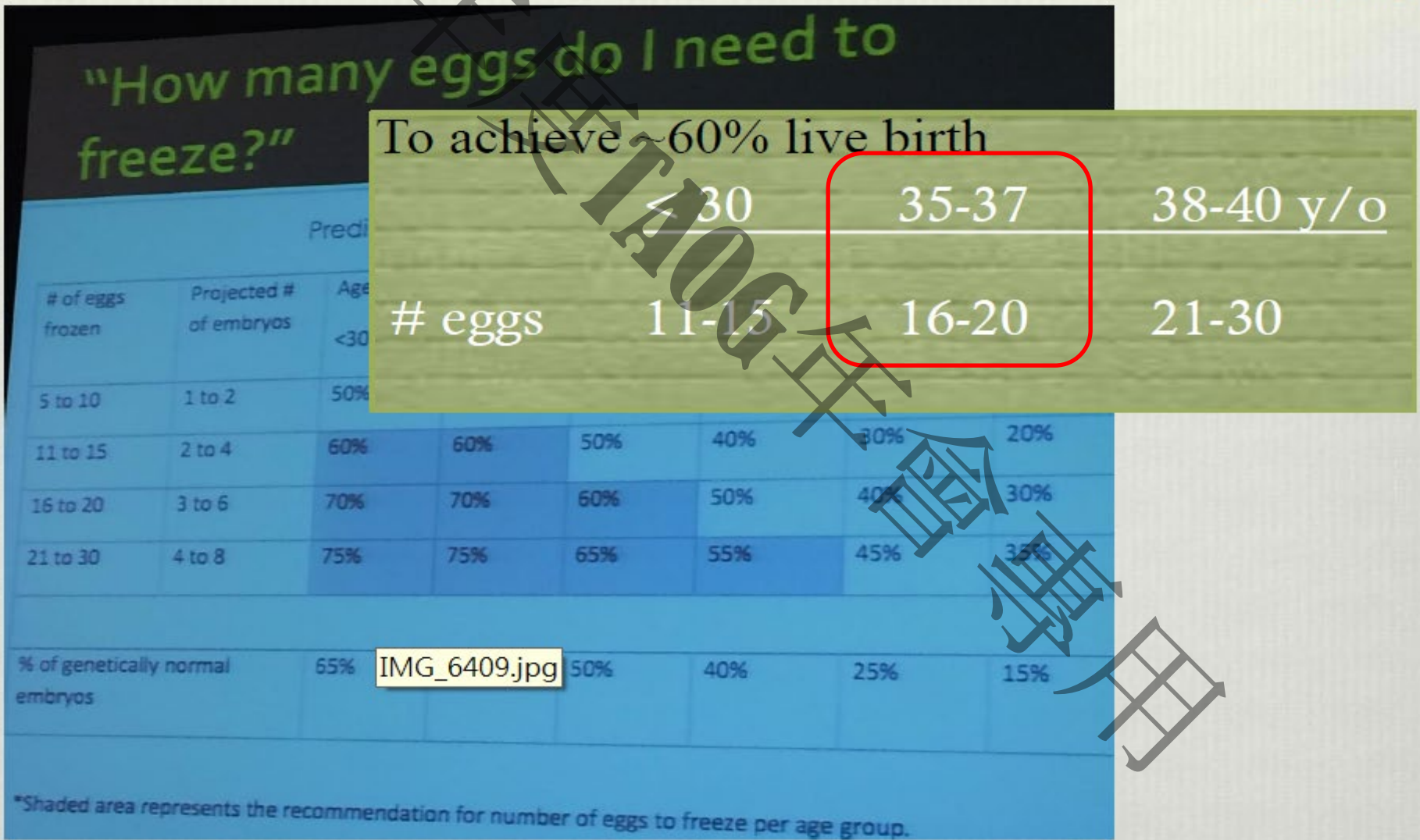


23,888 IVF cycles (212,009 mature oocytes) performed in Free University Hospital, Brussels between 1992 and 2009 .

Centre for Reproductive Medicine, UZ Brussel, Vrije Universiteit Brussel.

How many eggs do I need to freeze ?

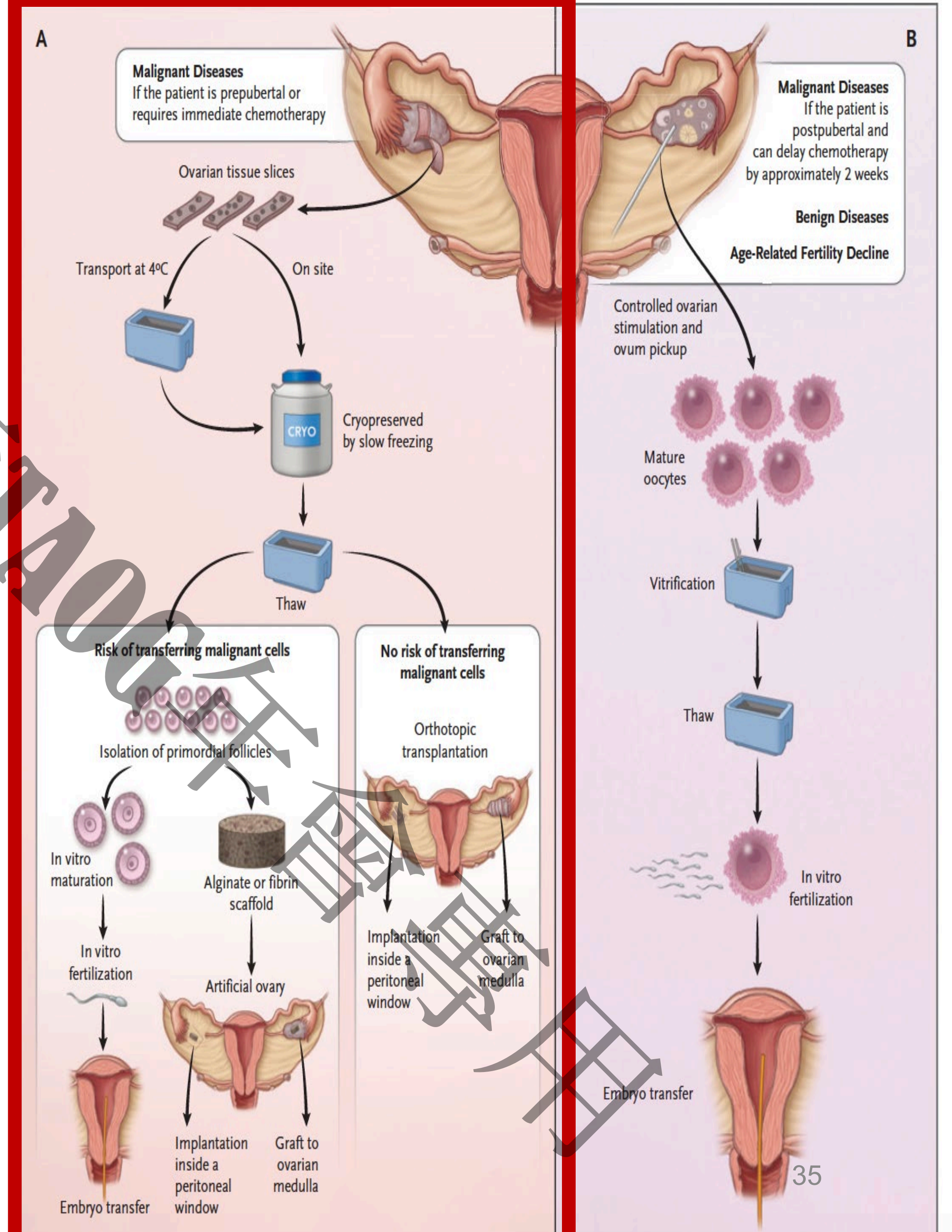
美國生殖醫學會觀點



Ovarian tissue cryopreservation

Ovarian tissue cryopreservation

- Need immediate chemotherapy
- Prepubertal



Ovarian tissue transplantation

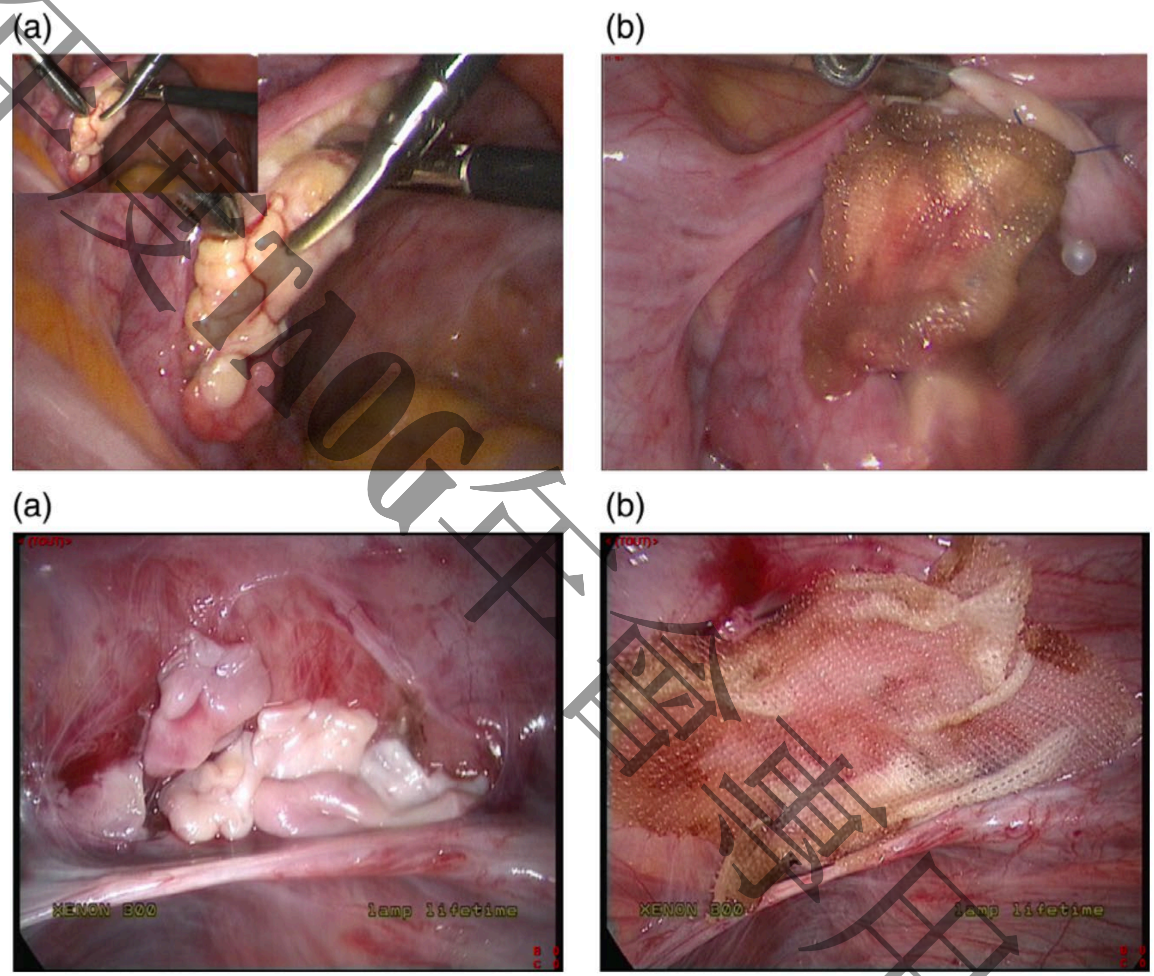


Figure 3 Techniques for ovarian tissue reimplantation. Frozen-thawed ovarian tissue fragments placed in a decorticated ovary (a) and subsequently covered with Interceed and fibrin glue (b). Peritoneal window created by means of scissors and ovarian cortex pieces (c), covered after with Interceed and fibrin glue. Medulla of each fragment has to be grafted facing and in contact with the denuded ovary (a) or the peritoneum (c) accordingly.

J. Obstet. Gynaecol. Res. Vol. 45, No. 2: 266–279, February 2019

台灣生殖醫學會對卵巢組織冷凍保存之立場聲明(2021)

- 美國生殖醫學會在2019年12月正式宣告OTC是一項可行的生育保存技術，而且不再被認為是實驗性質的技術 ，也是青春期前的女孩唯一可行的生育保存選項
- 國際生育保存學會(the International Society for Fertility Preservation, ISFP)及癌症生育集團(Oncofertility Consortium)自2019年12月之後也都同步認定OTC不再是實驗性質的治療方式。
- 從2004年以此技術的第一例活產在比利時誕生以來，目前超過300位已經接受冷凍組織解凍再植回手術，已經有180位嬰兒誕生
- 衡量目前世界上對於OTC/OTT用於生育保存之大趨勢，有鑑於此，台灣已確實有必須即刻迎頭趕上的迫切性

適用對象

- 緊急狀況下的癌症治療，當患者在治療後預期會有中度或高度不孕風險，而且沒有充分時間或完全不適合進行使用藥物刺激卵巢以便取卵及後續之卵子或胚胎冷凍保存
- 良性卵巢疾病而必須切除卵巢之時
- 青春期前的小女孩，這也是目前唯一可行的生育保存方法
- 血液癌症病人的安全性方面仍有疑慮
- 技術對高齡女性的成效並不理想，所以最適合的對象仍是36歲（含）以前的育齡女性

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Adverse outcomes associated with fertility preservation treatment

Research

JAMA Oncology | Original Investigation

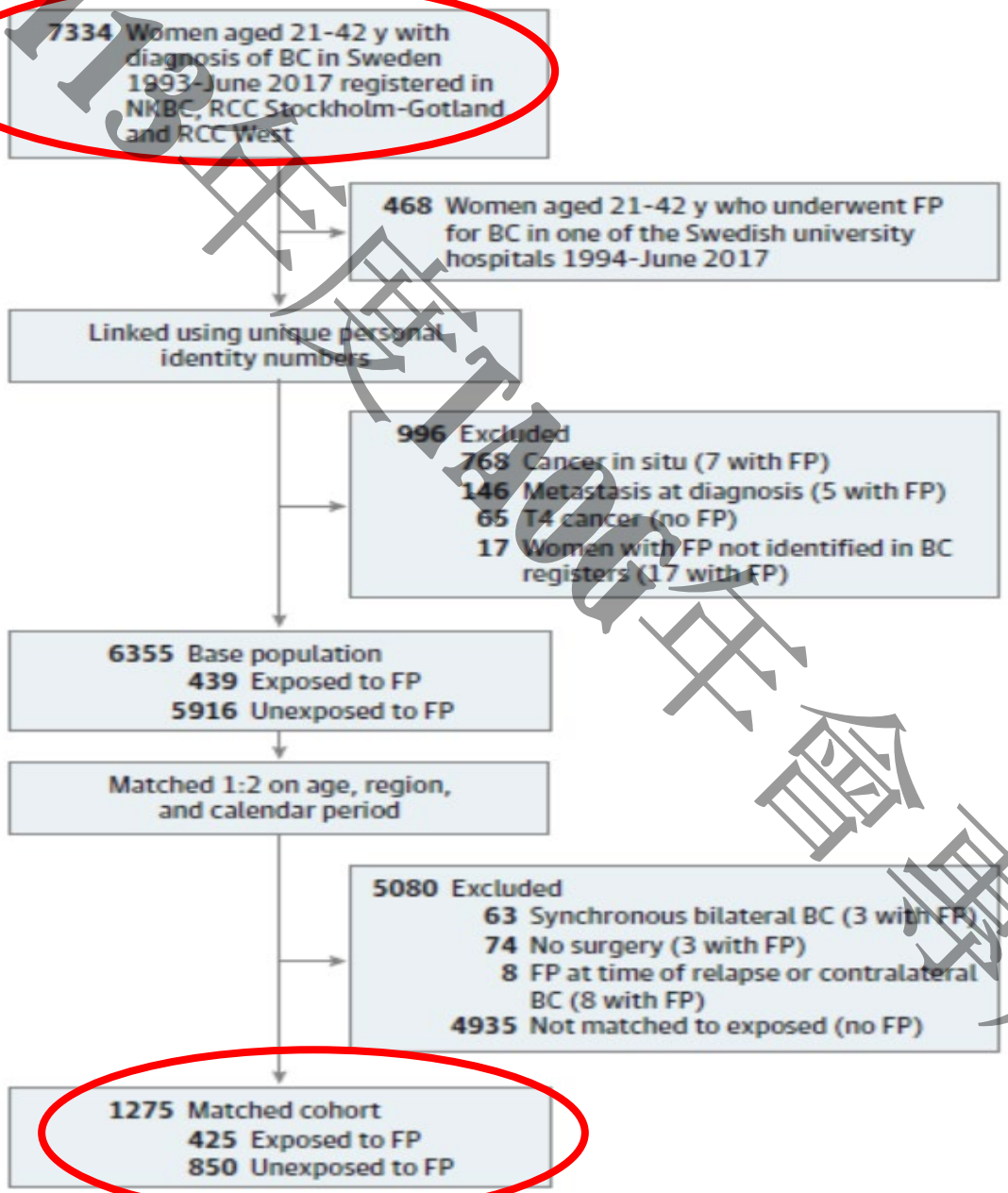
Relapse Rates and Disease-Specific Mortality Following Procedures for Fertility Preservation at Time of Breast Cancer Diagnosis

Anna Marklund, MD, PhD; Tobias Lekberg, MD; Elham Hedayati, MD, PhD; Annelie Liljegren, MD, PhD; Jonas Bergh, MD, PhD; Frida E. Lundberg, PhD; Kenny A. Rodriguez-Wallberg, MD, PhD

Supplemental content

JAMA Oncol. 2022 Oct 1;8(10):1438-1446

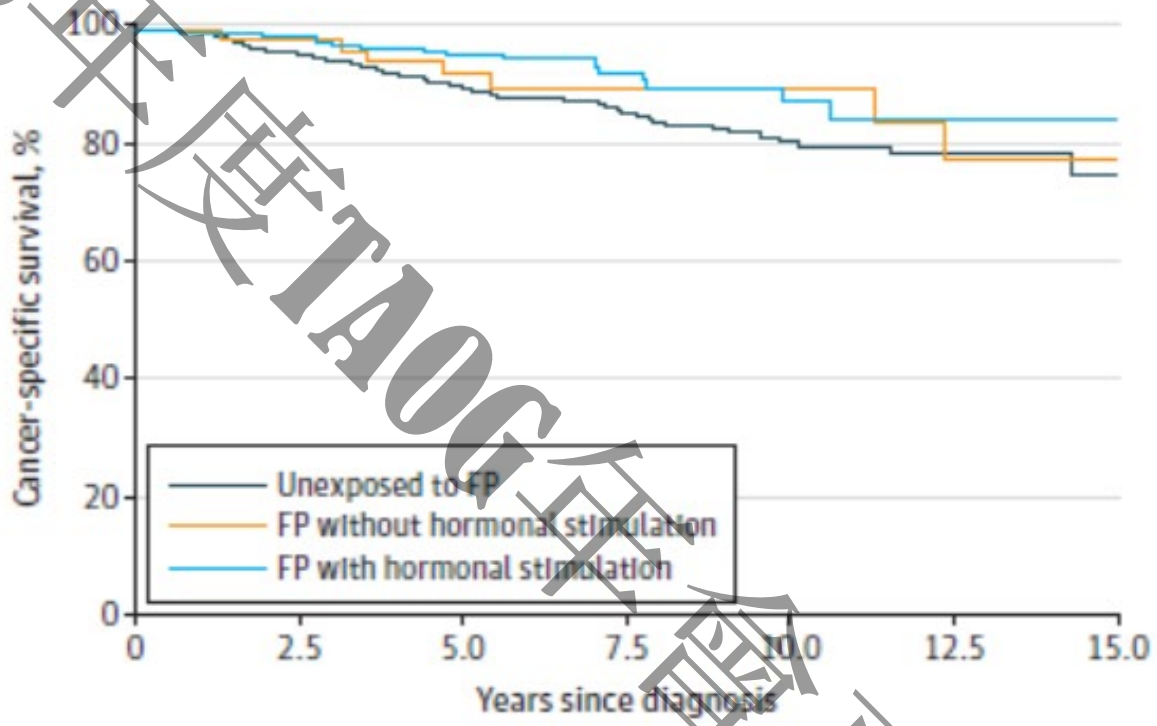
Adverse outcomes associated with fertility preservation treatment



JAMA Oncol. 2022 Oct 1;8(10):1438-1446

Adverse outcomes associated with fertility preservation treatment

Figure 2. Cancer-Specific Survival in the Cohort



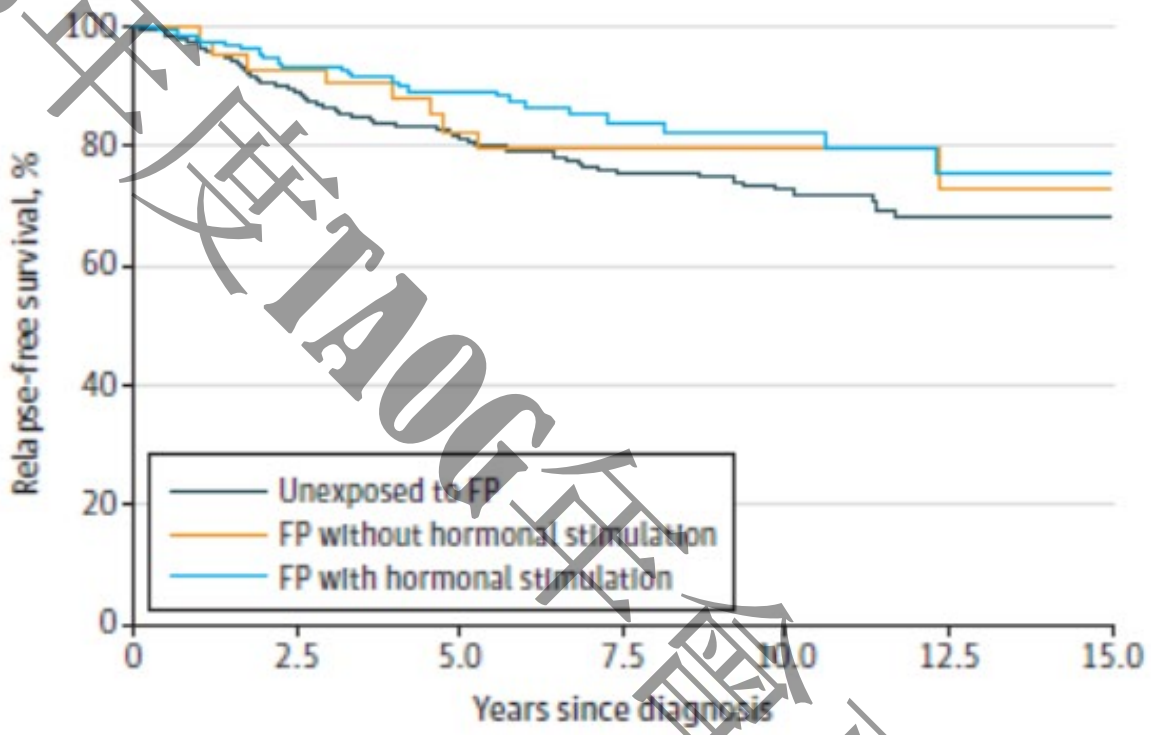
No. at risk

Unexposed	850	576	349	175	98	50	17
FP without stimulation	58	55	41	25	19	11	4
FP with stimulation	367	267	138	73	35	21	11

JAMA Oncol. 2022 Oct 1;8(10):1438-1446

Adverse outcomes associated with fertility preservation treatment

Figure 3. Relapse-Free Survival in the Subcohort



No. at risk							
Unexposed	482	349	247	143	88	50	16
FP without stimulation	43	39	29	21	17	10	4
FP with stimulation	198	157	105	60	32	17	9

JAMA Oncol. 2022 Oct 1;8(10):1438-1446

Adverse outcomes associated with fertility preservation treatment

- In this cohort study, FP with or without hormonal stimulation was not associated with any increased risk of relapse or disease-specific mortality in women with breast cancer.

JAMA Oncol. 2022 Oct 1;8(10):1438-1446

Adverse outcomes associated with fertility preservation treatment

European Journal of Cancer 174 (2022) 134–141

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Efficacy and safety of controlled ovarian hyperstimulation with or without letrozole for fertility preservation in breast cancer patients: A multicenter retrospective study

Oranite Goldrat [a,*], Manon De Cooman [b], Audrey Mailliez [c], Anne Delbaere [a], Emmanuelle D'Orazio [d], Isabelle Demeestere [a,c], Christine Decanter [d]

[a] Fertility Clinic, Department of Obstetrics and Gynecology, CUB Erasme Hospital, Université Libre de Bruxelles (ULB), Route de Lennik 808, 1070 Brussels, Belgium

Eur J Cancer. 2022 Oct:174:134-141

Adverse outcomes associated with fertility preservation treatment

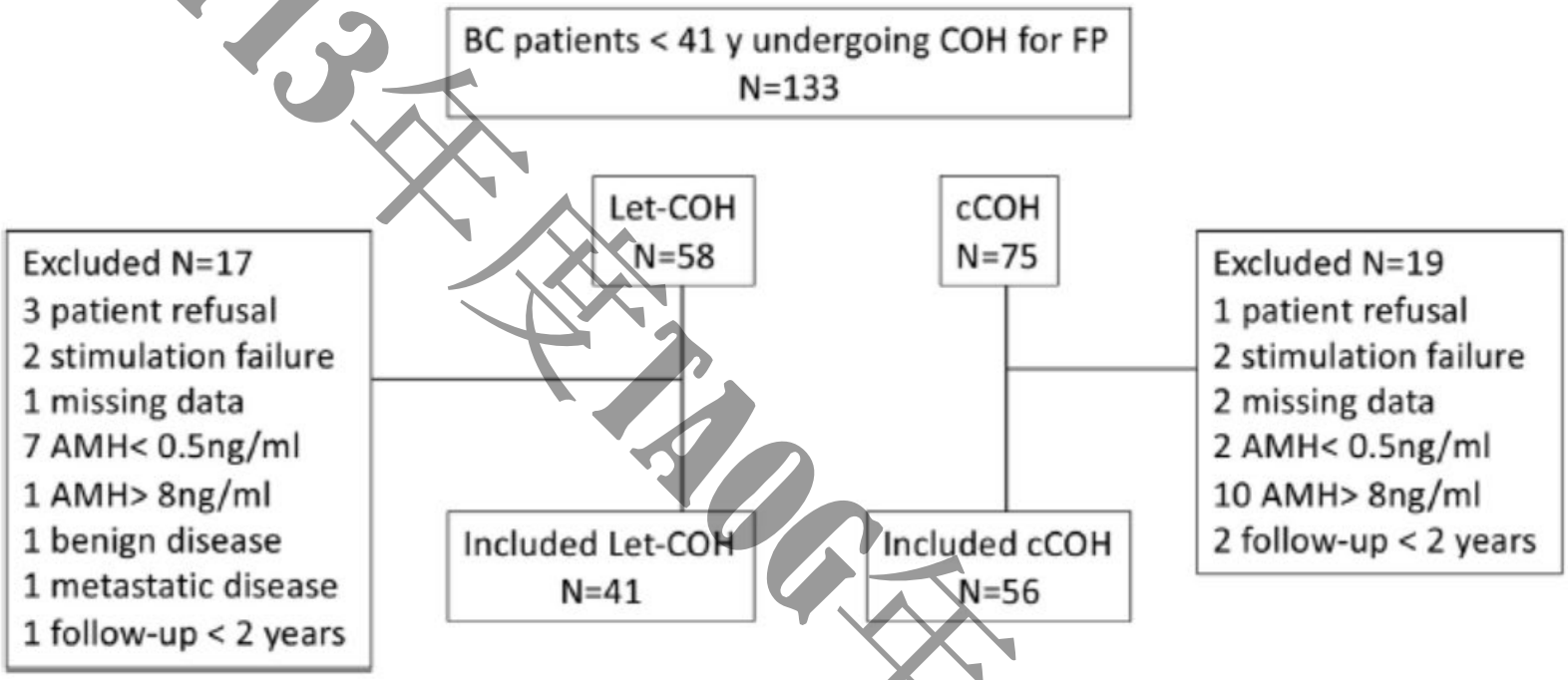


Fig. 1. Flowchart. Abbreviations: AMH: anti-mullerian hormone, BC: breast cancer, LetCOH: letrozole-associated controlled ovarian hyperstimulation, cCOH: conventional controlled ovarian hyperstimulation.

Letrozole seems to be beneficial regarding the number of mature oocytes retrieved while minimizing the risk of supraphysiologic estrogen exposure. At this time point, there were no safety concerns regarding cCOH in the adjuvant setting but a longer follow-up is warranted.

Eur J Cancer. 2022 Oct:174:134-141

Adverse outcomes associated with fertility preservation treatment

Received: 18 June 2021 | Revised: 29 October 2021 | Accepted: 1 December 2021

DOI: 10.1002/ijc.33933

CANCER THERAPY AND PREVENTION

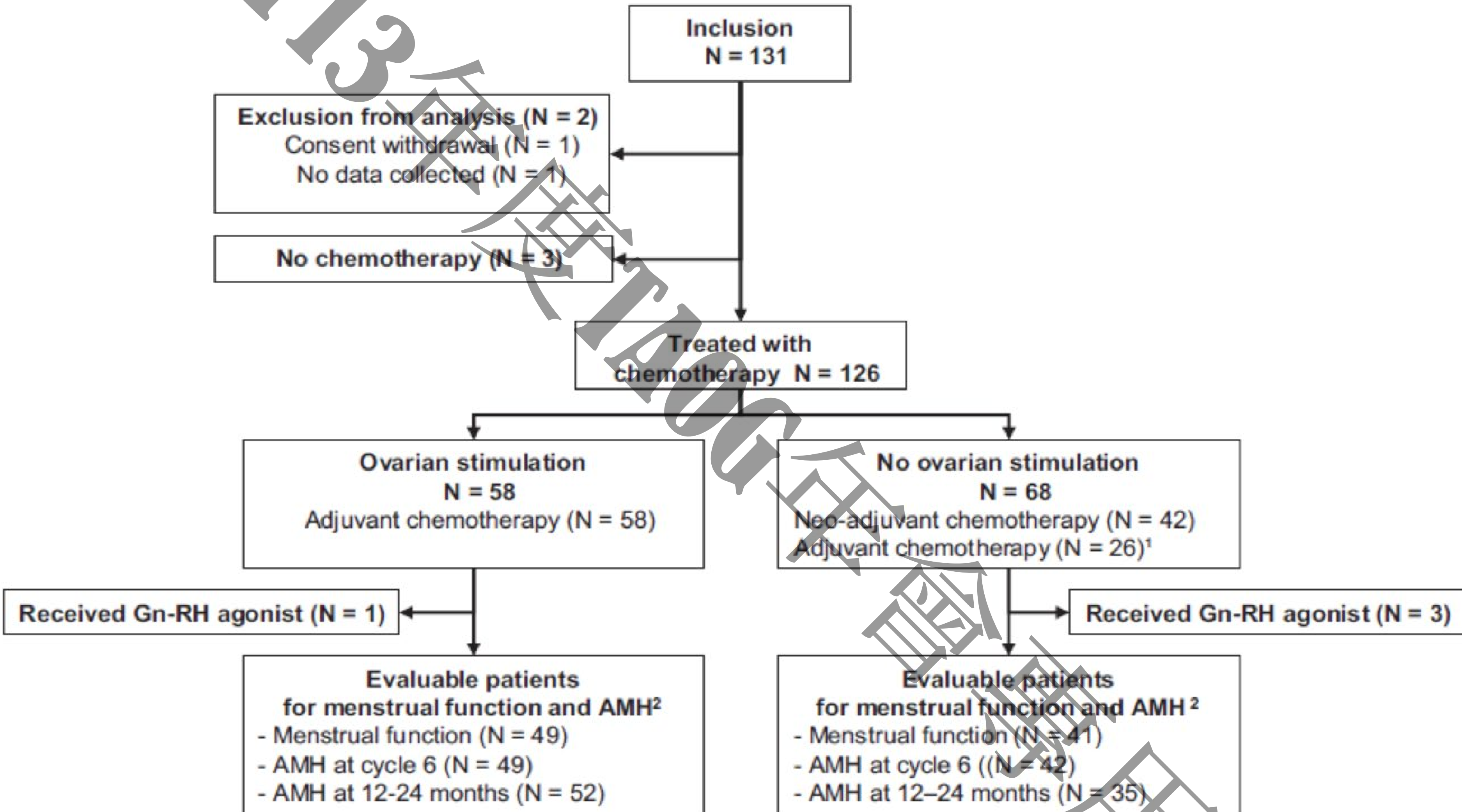
IJC INTERNATIONAL JOURNAL of CANCER

Is ovarian recovery after chemotherapy in young patients with early breast cancer influenced by controlled ovarian hyperstimulation for fertility preservation or tumor characteristics? Results of a prospective study in 126 patients

Audrey Mailliez[1] | Pascal Pigny[2,3] | Emilie Bogart[4] | Laura Keller[5] | Emmanuelle D'Orazio[6] | Marie Vanseymortier[4] | Marie-Cécile Le Deley[4] | Christine Decanter[6,7]

Int J Cancer. 2022 Jun 1;150(11):1850-1860

Adverse outcomes associated with fertility preservation treatment



Int J Cancer. 2022 Jun 1;150(11):1850-1860

Adverse outcomes associated with fertility preservation treatment

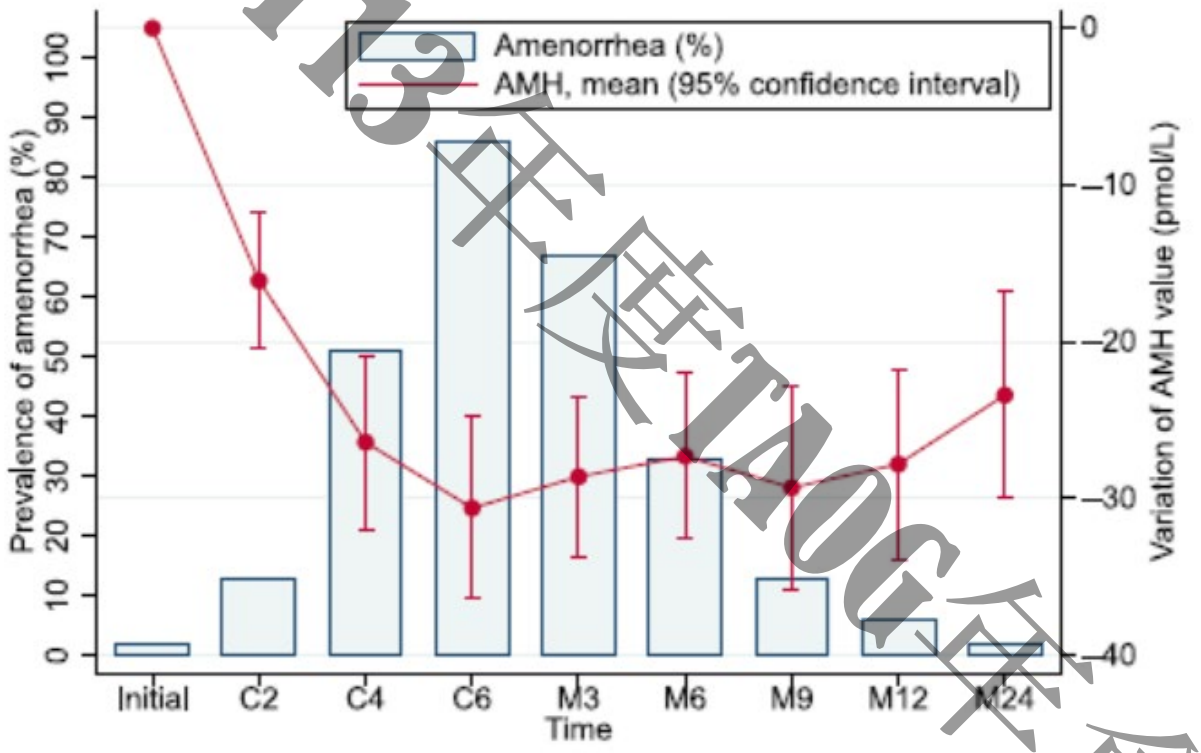


FIGURE 2 Evolution of prevalence of amenorrhea and mean AMH level over time. Patients received six courses of chemotherapy over a 18-week period. Measurements were performed at the beginning of the 2nd cycle (C2), 4th cycle (C4) and 6th cycle (C6), then every 3 months after the end of chemotherapy for 1 year (M3, M6, M9 and M12), and finally 24 months after the end (M24) of chemotherapy

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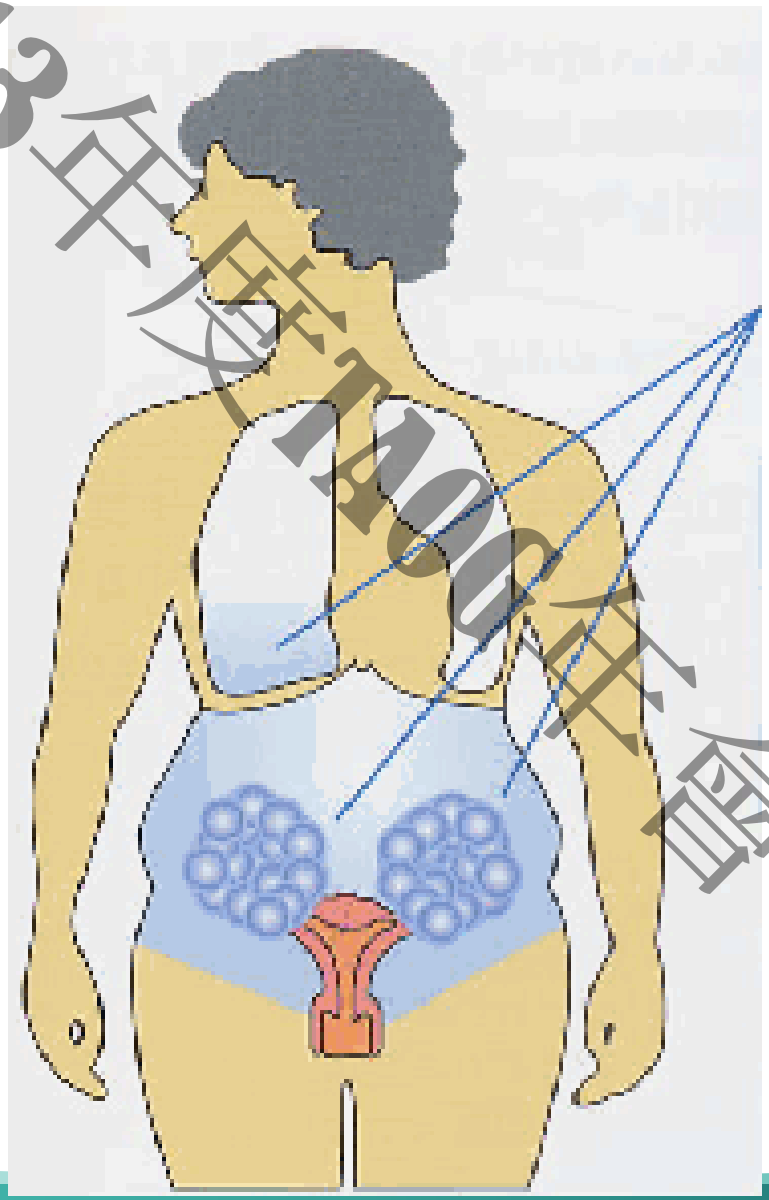
Adverse outcomes associated with fertility preservation treatment

- Serum **AMH** is a marker of ovarian follicular content and a real-time indicator of both follicular depletion and ovarian recovery in patients with cancer.
- The findings indicate that **sequential chemotherapy** is associated with a higher risk of persistent amenorrhea.
- There was **no significant association** between tumor characteristics, fertility preservation with controlled ovarian hyperstimulation or recovery of the ovarian reserve.
- The study underlines the necessity of **fertility preservation** before commencing chemotherapy.

Int J Cancer. 2022 Jun 1;150(11):1850-1860

卵巢過度刺激症候群(OHSS)



肺部積水

腹水

卵巢腫大

Concept

1. Background
2. When ?
3. How ?
4. Risky ?
5. Ethical issue
6. Suggestion

生殖細胞之保存

- **人工生殖機構歇業時，其所保存之生殖細胞或胚胎應予銷毀。**
- 但經捐贈人書面同意，其所 捐贈之生殖細胞，得轉贈其他人工生殖機構
- 受術夫妻之生殖細胞或胚胎，經受術夫妻書面同意，得轉其他人工生殖機構繼續保存。

生殖細胞之保存

- 醫療機構應申請主管機關許可後，始得實施人工生殖、接受生殖細胞之捐贈、儲存或提供之行為。
- 公益法人應申請主管機關許可後，始得接受精子之捐贈、儲存或提供之行為。

人工生殖醫學法

The Ethics of Egg Freezing
Reproductive autonomy versus well-being of the child

- More older parents

Neonatal and maternal risks increased of at an advanced maternal age

Among women aged 50–65 years, 68.5% of the infants have a LBW.

Older parents can provide **advantages**, such as: relational stability, parent-child interactions and financial situation

- More IVF-related births

Significant more malformation in children conceived after IVF-ICSI

Elevated risk for preterm birth even in singletons after IVF

Swiss Med Wkly. 2013;143:w13746

Concept

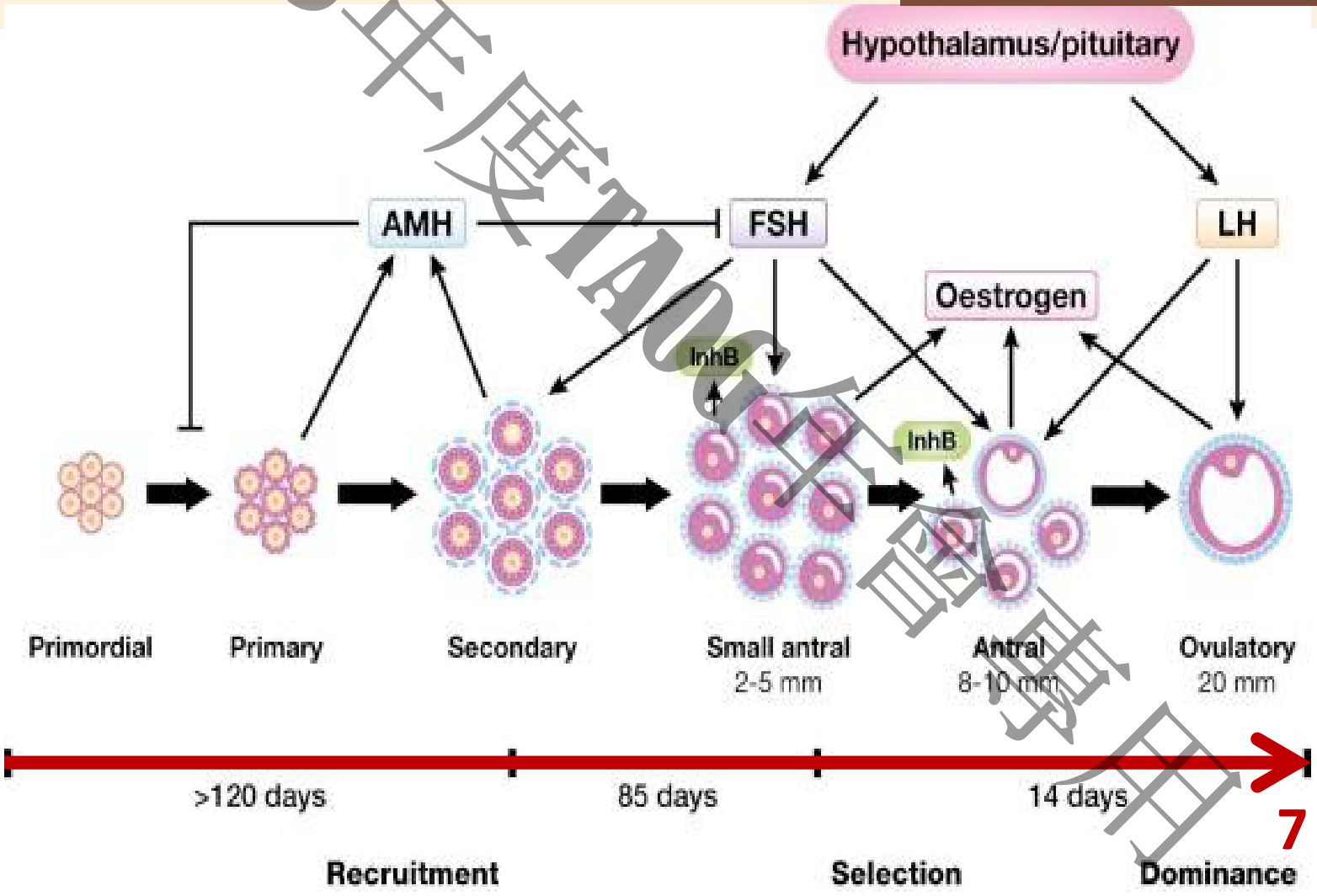
1. Background
2. When ?
3. How ?
4. Risky ?
5. Ethical issue
6. Suggestion

Take home message

- **Ovarian damage from chemotherapy**
  - Primordial follicle → direct loss/ indirect loss
  - Antral follicle → vascular damage
  - Alkylating agent : Cyclophosphamide
- **Fertility preservation**
  - Cryopreservation → embryo, oocyte, ovarian tissue
  - GnRH analogue
- **Efficacy of IVF with the timing of chemotherapy**
  - Before chemotherapy
  - Immediately after chemotherapy → ovarian tissue cryopreservation
  - After chemotherapy → interval >6 months to 1 year

Folliculogenesis

Int. J. Mol. Sci. 2019, 20, 4720
Front Endocrinol . 2022 Oct 24;13:985525
Gynecol Endocrinol. 2022 Nov 20;1-6.
BMC Womens Health. 2022 Nov 7;22(1):436



7 months

來自病患的回應或回饋

1. 我相信生育力保存對我可能很重要，但是它的代價可能不是我能負擔，希望能有比較簡單的方法即使效果沒有那麼完整
2. 我暫時還沒有辦法釐清生育力保存對我的意義，但還是希望轉介生殖醫學中心聽取專家建議
3. 我暫時還沒有辦法釐清生育力保存對我的意義，但希望能有比較簡單的方法保留，即使效果沒有那麼完整
4. 生育能力的保留對現在與將來的我，都不是那麼重要 ……………………

結論與建議

Disease-focused
Fertility preservation

Practical flow

- 生育保存需求
  - Hormone assay (AMH, FSH, E2)
  - 住院病人
    - 會診婦產部 --生殖內分泌科
    - 指定會診至 生殖內分泌科(不孕症)門診
  - 門診病人
    - 生殖內分泌科(不孕症)門診

113年度TAOG年會專用

生殖細胞 卵子精子 生育保存治療

科內官網連結

臉書連結

長庚生殖醫學中心
林口長庚醫院兒童大樓K棟12樓
諮詢電話：03-328-1200 # 2709 或 2712 或2713

女性生育保存療程

01 ＊抽血檢驗
評估卵巢功能,基礎荷爾蒙
＊超音波檢查
子宮,卵巢結構,基礎濾泡數量

02 門診諮詢

03 進入療程
▼
卵巢刺激
▼
取卵手術(約需兩週)

04 後續癌症治療

男性生育保存流程

貼心提示

- 越早進入生育保存治療的病患,越能確保治療後的生育能力。
- 對於具有雌激素敏感的癌症病患,亦有適合的生育保存方式。
- 若有欲接受治療或有相關疑問,請洽詢生殖醫學中心或您的癌症治療團隊。

The future

Thank You