

## Postsurgical barrier strategies to avoid the recurrence of intrauterine adhesion formation after hysteroscopic adhesiolysis: a network meta-analysis of randomized controlled trials



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John Preston Parry, MD, MPH; Attilio Di Spiezio Sardo, MD, PhD;  
Pasquale De Franciscis, MD, PhD

**PGY2** 張千奕

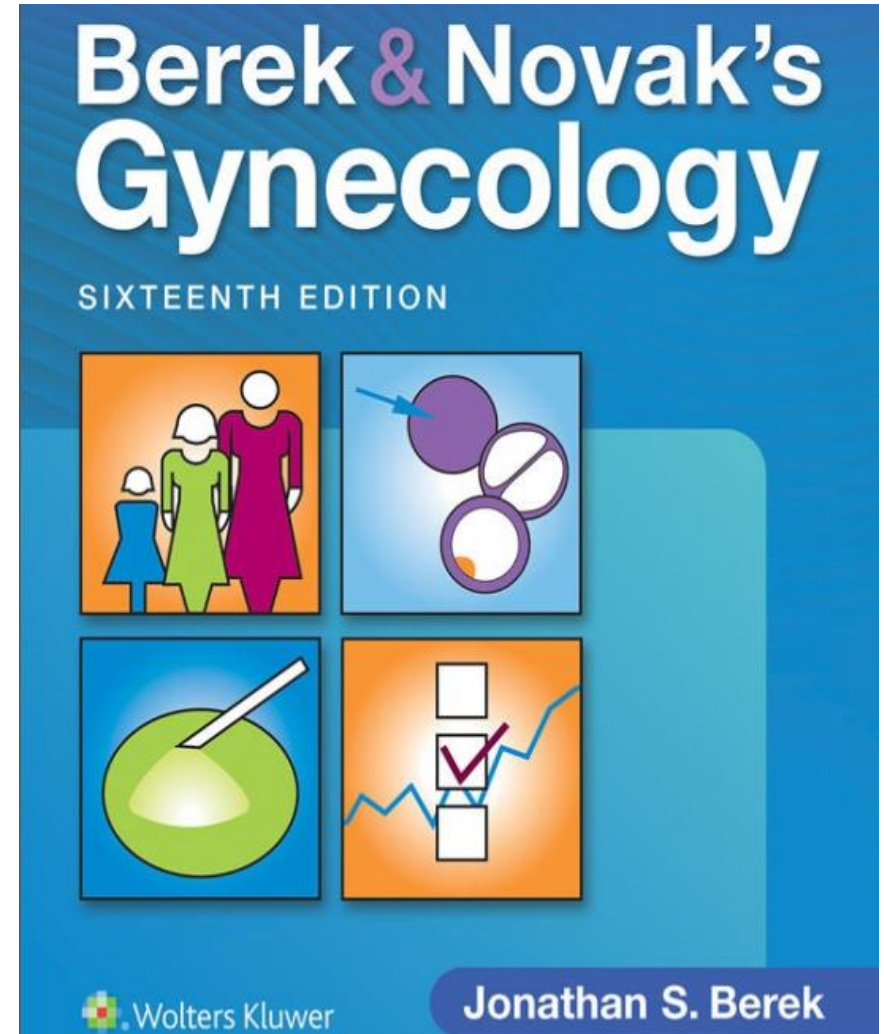
**Supervisor:** 施胤竹 醫師

0.

# Table of contents



- 1. Operative Hysteroscopy**
- 2. Journal reading**



1-1.

# Operative Hysteroscopy

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# **Intrauterine procedures**

- **adhesiolysis**
- **resection of leiomyomas and polyps**
- **endometrial ablation**
- **transection of uterine septum**

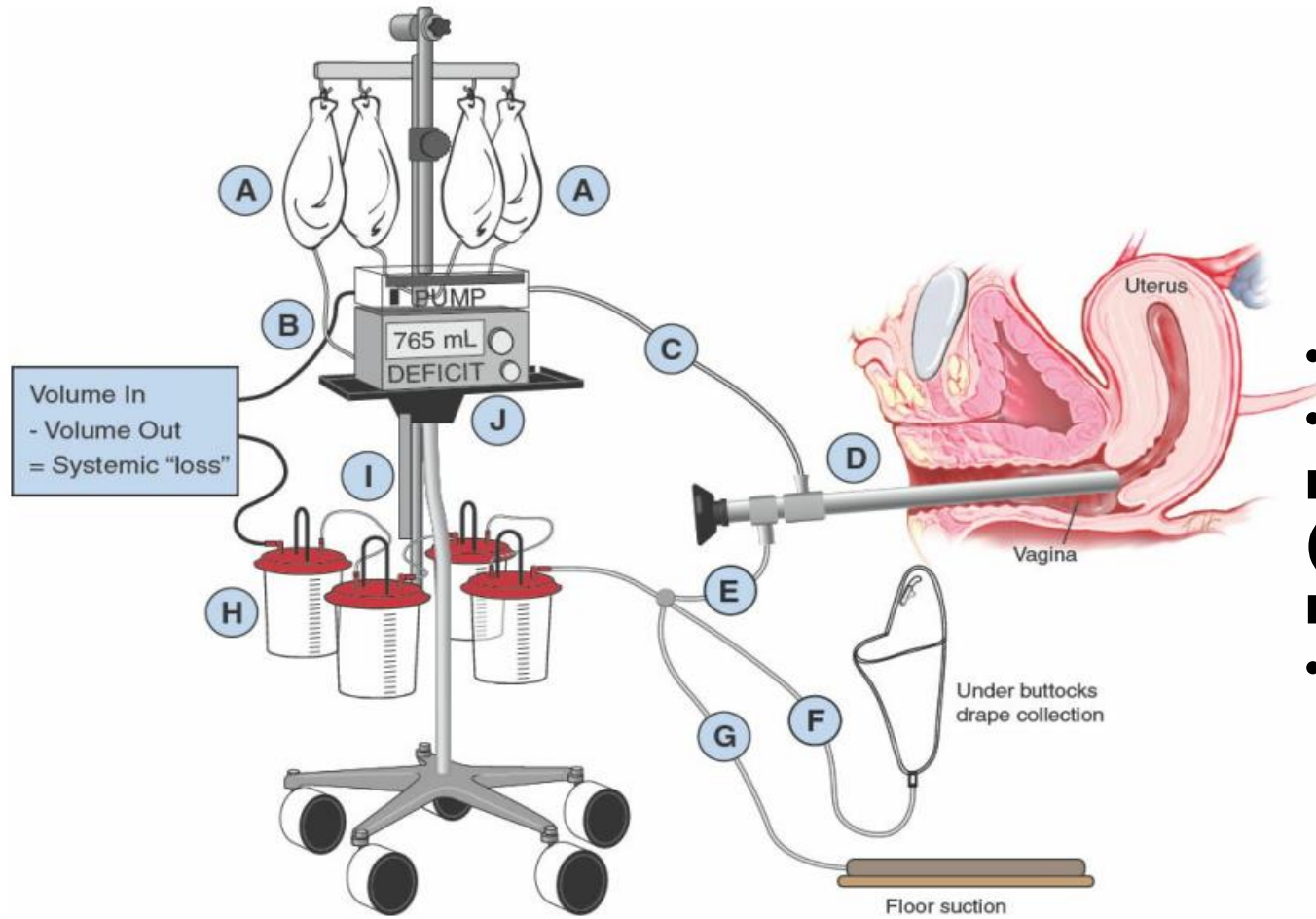
# **Core competencies for hysteroscopy**

- **Patient positioning and cervical exposure**
- **Anesthesia**
- **Cervical dilation**
- **Uterine distention**
- **Visualization and imaging**
- **Intrauterine cutting and hemostasis**
- **Other instrumentation**

# Core competencies for hysteroscopy

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# Core competencies for hysteroscopy



- monopolar / bipolar electrodes
- **Monopolar:**  
nonconducting distending solution  
(sorbitol 5%, sorbitol 3% with  
mannitol 0.5%, or glycine 1.5%)
- **Bipolar: saline.**

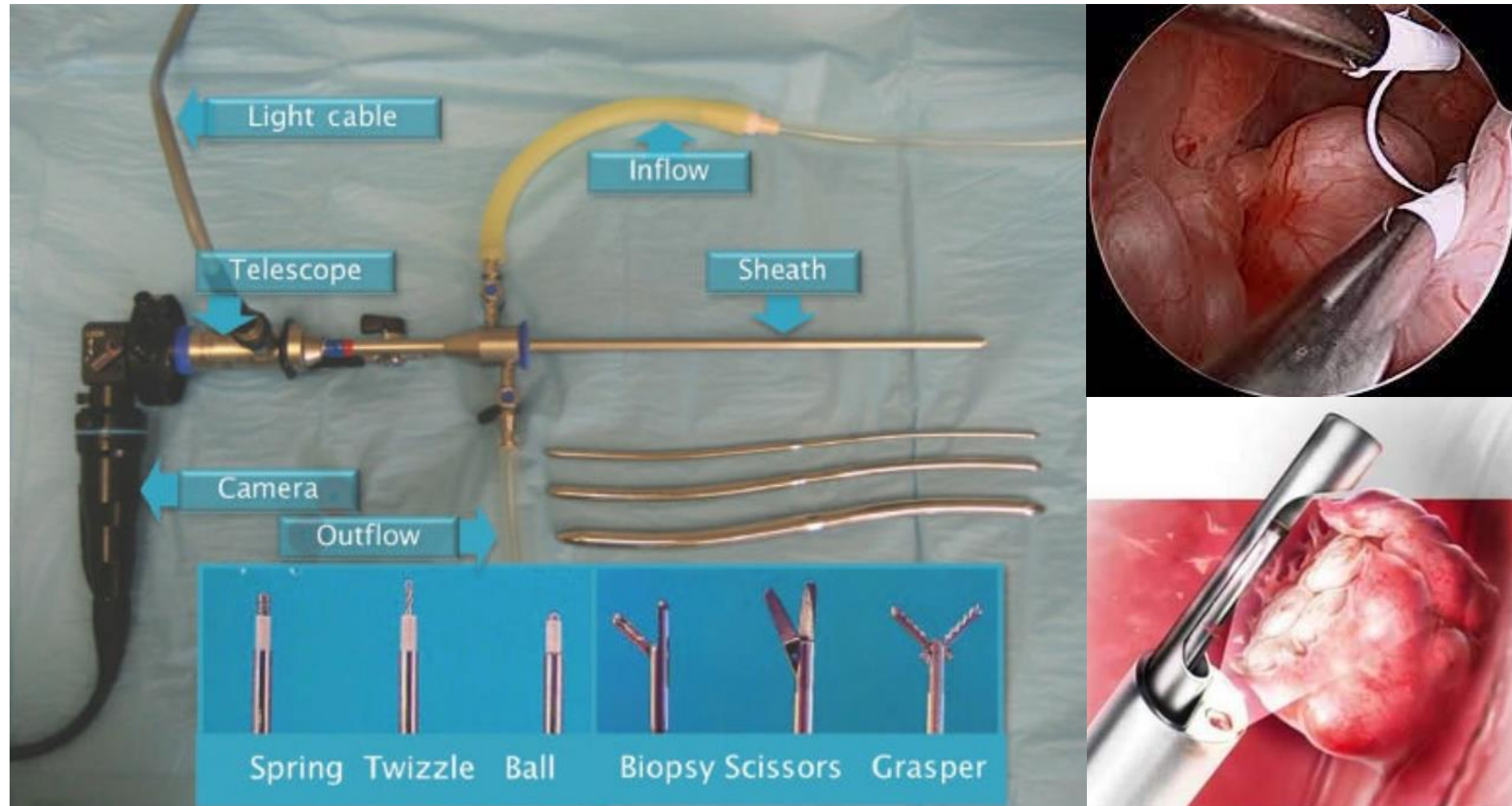
**FIGURE 26-47** Fluid management system.



# Core competencies for hysteroscopy

- Patient positioning and cervical exposure
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# Core competencies for hysteroscopy

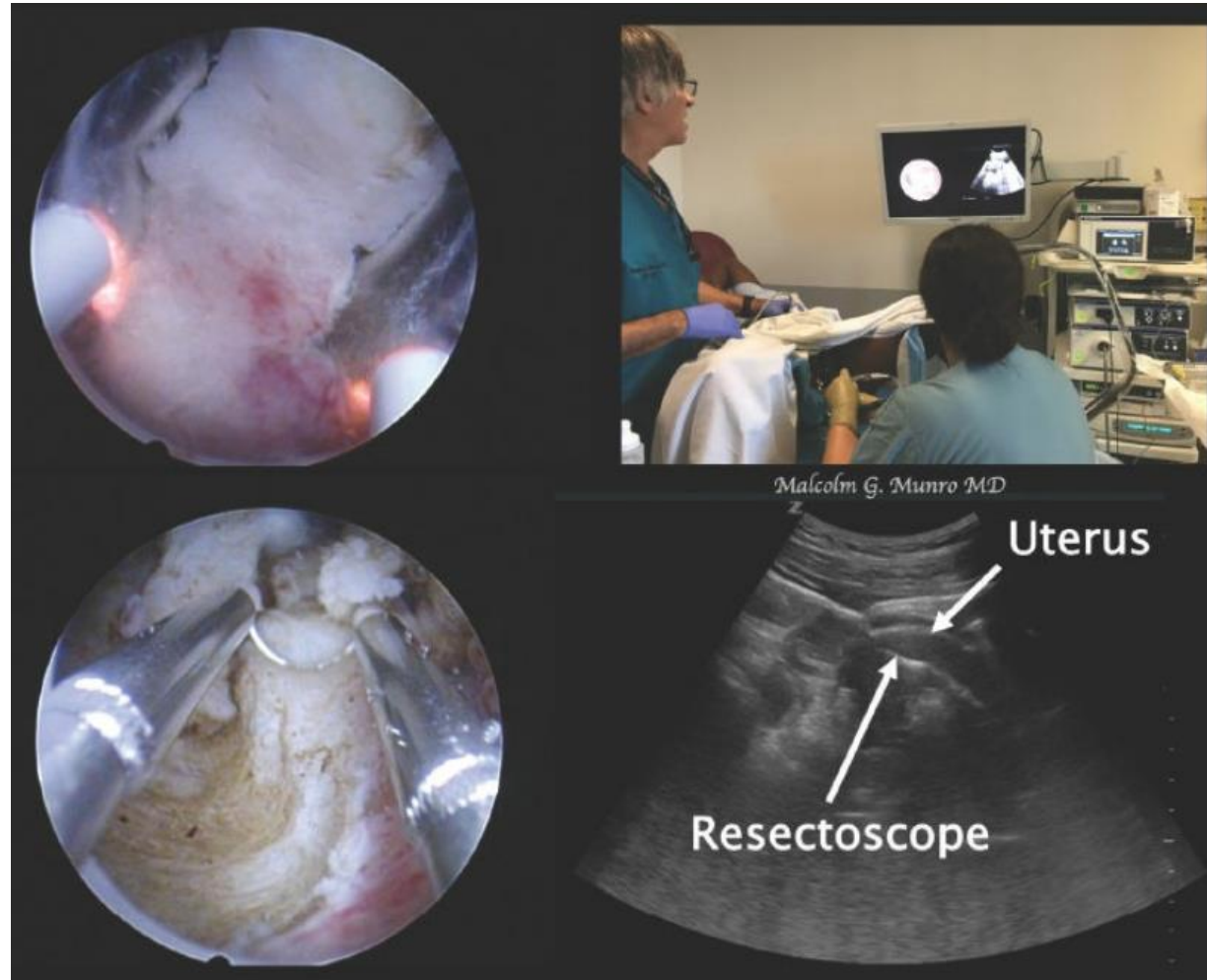


**FIGURE 26-44** Office hysteroscopy instruments.

# Core competencies for hysteroscopy

- Patient positioning and cervical exposure
- Anesthesia
- Cervical dilation
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- **Other instrumentation**

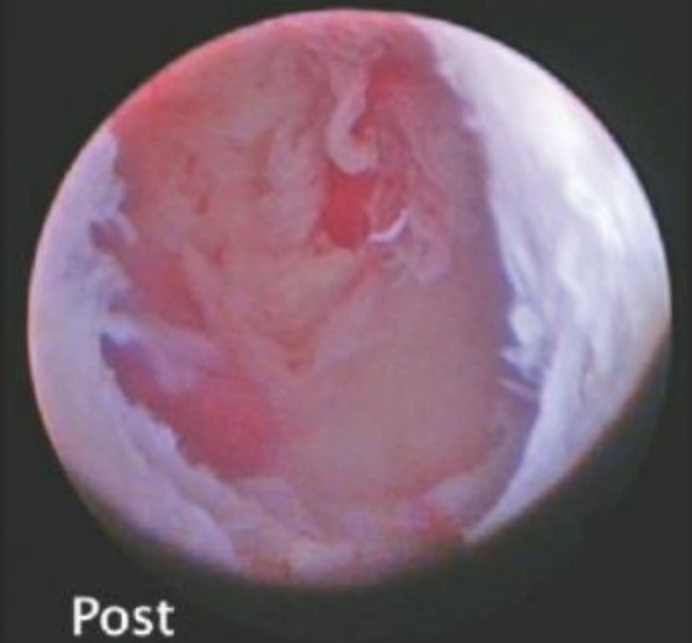
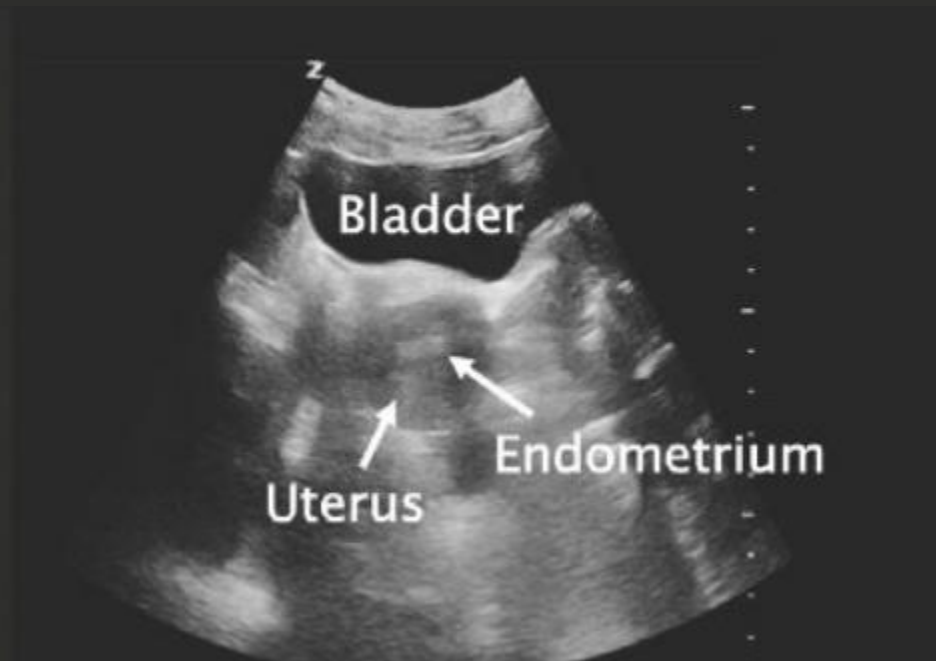
# Core competencies for hysteroscopy



**FIGURE 26-51** Simultaneous hysteroscopic and transabdominal ultrasound imaging.

# Synechia

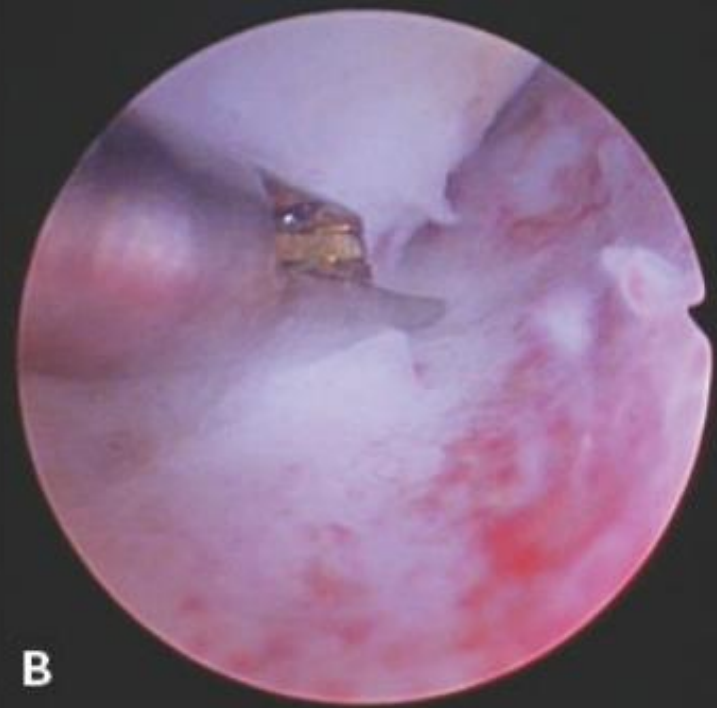
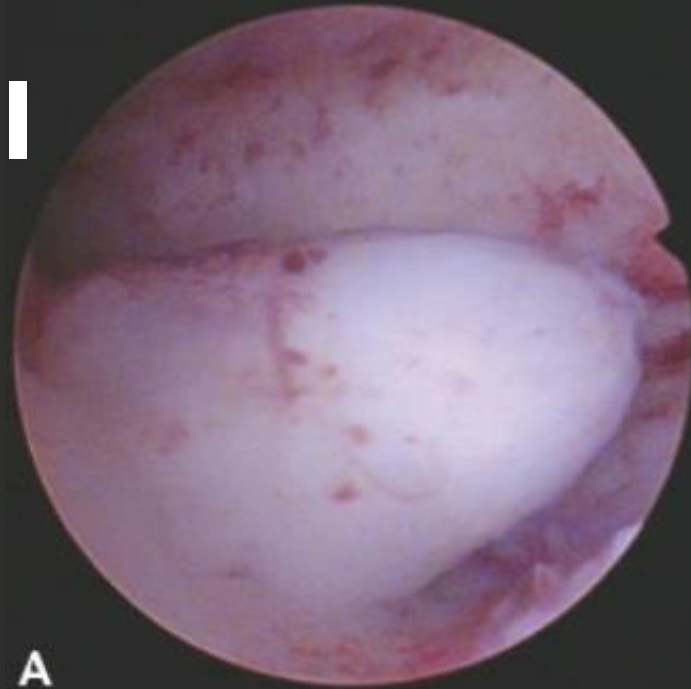
## Asherman syndrome





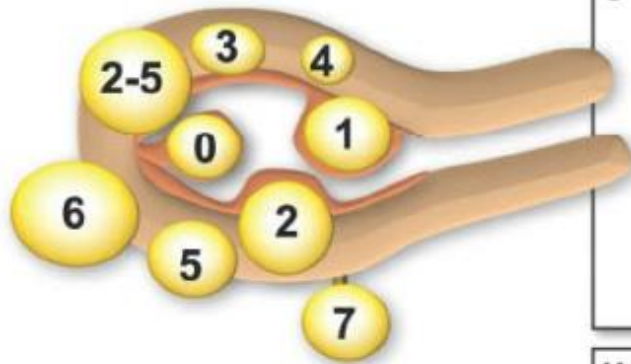
# Endometrial Polyps

Endometrial polypectomy



# Leiomyomas

## Leiomyoma subclassification system



<b>SM - Submucous</b>	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
<b>O - Other</b>	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserous ≥50% intramural
	6	Subserous <50% intramural
	7	Subserous pedunculated
	8	Other (specify e.g., cervical, parasitic)
<b>Hybrid leiomyomas (contact both the endometrium and the serosal layer)</b>	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucous and subserous, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

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# Myomectomy

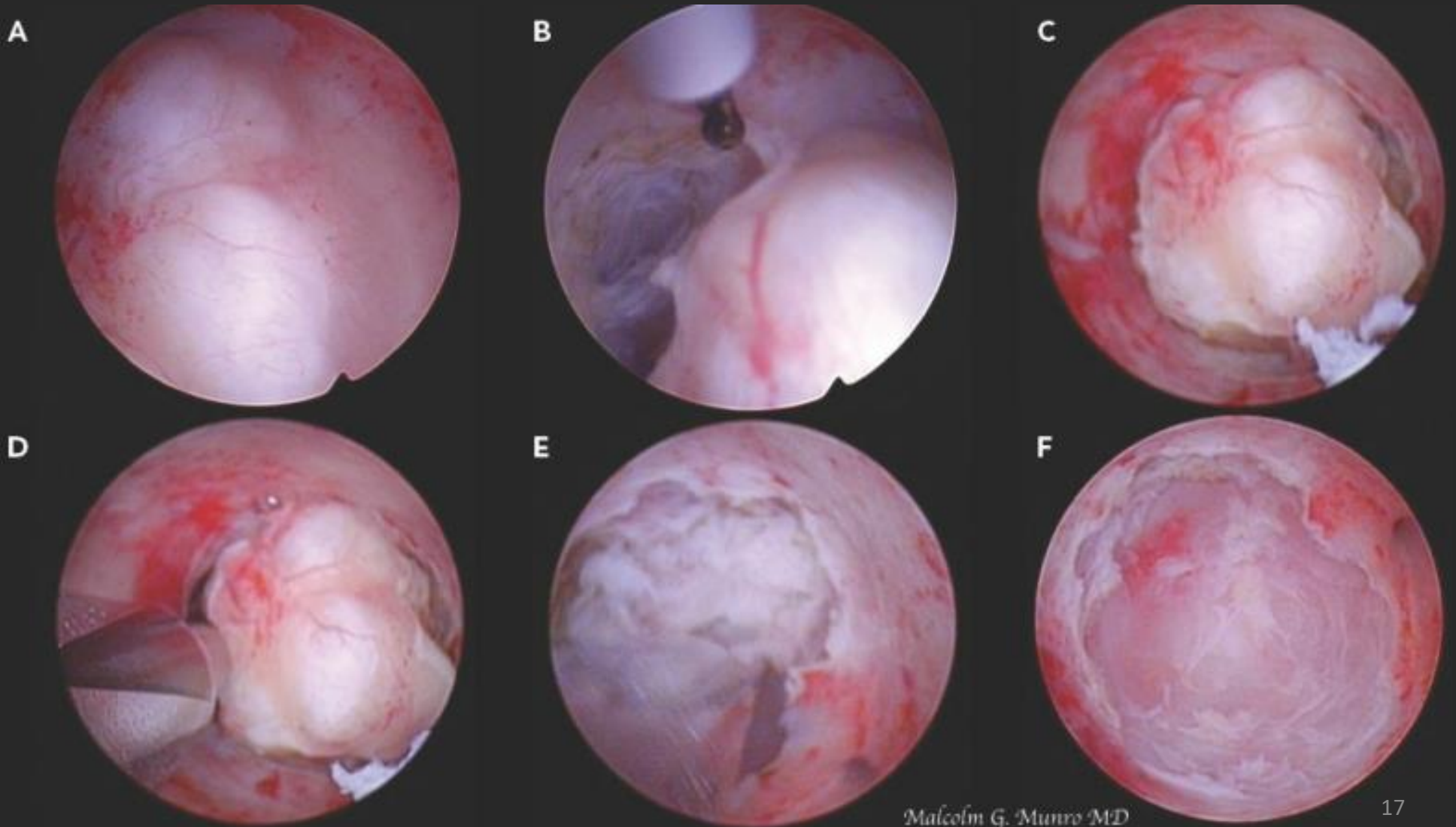
FIGO type 0  
leiomyoma





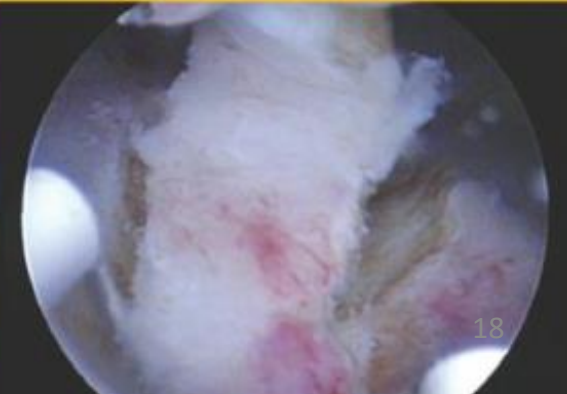
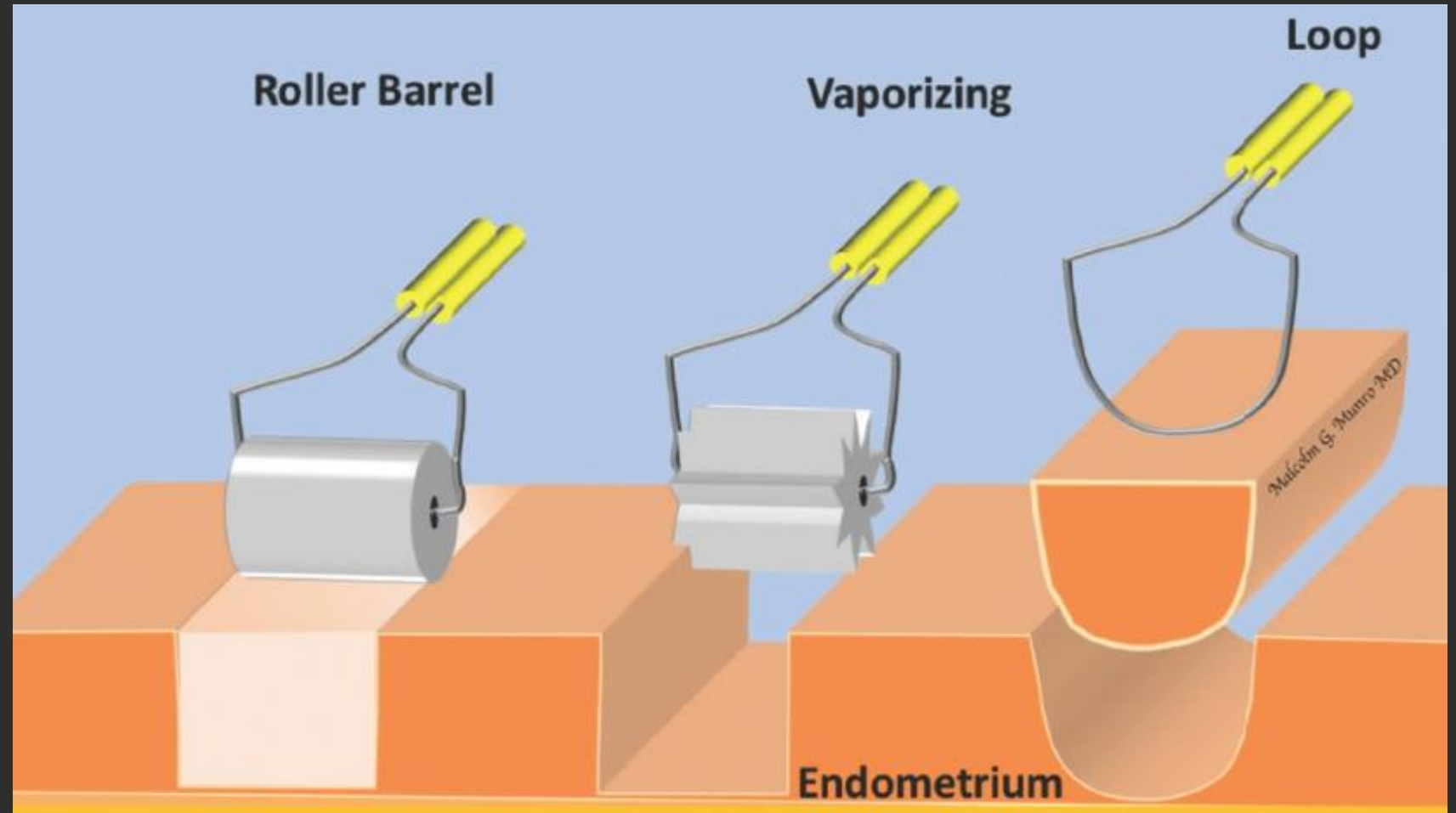
# Myomectomy

FIGO type 2  
leiomyoma



# Endometrial Ablation

Resectoscopic endometrial ablation (REA) techniques



# Septum

Transection of  
uterine septum



1-2.

# Complications



# **Uterine perforation / bowel, bladder injury**

- **Cervical dilatation**
- **Hysteroscope insertion**
- **G2 fibroids**
  
- **Pre-op evaluation(SIS or MRI)**
- **simultaneous ultrasound**
- **repeat resection after a few weeks**
  
- **fluid deficit**
- **brisk bleeding**

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# Fluid Absorption/Electrolyte Imbalance

- **absorption of distending media**
- **pulmonary edema**
- **hyponatremia**
- **Heart failure**
- **cerebral edema**
- **Death**
- **Warning: 750 mL**
- **Termination: 1,000 mL**  
(1500mL nonelectrolyte/2,500 mL electrolyte)



# Fluid Absorption/Electrolyte Imbalance

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# 2-1.

# Introduction



# **What is IUA? (Intrauterine adhesions)**

- **injury to the basalis layer of endometrium**
- **intracavitary granulation**
- **fibrous tissue bridges inside uterine cavity**

## **Causes**

### **D&C after**

- **postpartum hemorrhage**
- **pregnancy loss**
- **induced abortion**

# **Symptoms/Signs**

- **Menstrual pattern alterations (hypomenorrhea, amenorrhea)**
- **Dysmenorrhea**
  
- **Chronic pelvic pain**
  
- **pregnancy loss(up to 90%)**
- **placenta accreta**
- **preterm delivery**

# **IUA diagnosis/treatment**

**Gold standard: hysteroscopy**

- **Direct visualization**
- **Mechanical /electrosurgical adhesion lysis**

## **Challenging issue**

- **moderate or severe IUA**
- **recurrence of the adhesion:  
3-25%(up to 60 %)**

# Preventive strategies

- **copper intrauterine device (IUD)**
- **balloon catheter(±amnion grafts covering)**
- **hyaluronic acid(HAG)**

2-2.

**Objective:**

**Effect on subsequent outcomes**

2-3.

**Methods**



# **Data sources/search strategy**

- **Data base**
  - **MEDLINE , Scopus, EMBASE, Scielo.br, PROSPERO**
- **MeSH terms**
  - **Hysteroscopy**
  - **hysteroscopic adhesiolysis**
  - **intrauterine adhesions**
  - **Asherman syndrome**



# Inclusion criteria

- **randomized clinical trial**
- **Moderate-severe IUA**
  - **AFS score**(American Fertility Society)  $\geq 5$
- **hysteroscopic adhesiolysis +at least 1 mechanical antiadhesion treatment**

# Exclusion criteria

- quasi-randomized trials
- trials without randomization
- Not adhesiolysis

# Inclusion criteria

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- **Moderate-severe IUA**
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**TABLE 6**  
**THE AMERICAN FERTILITY SOCIETY CLASSIFICATION OF INTRAUTERINE ADHESIONS**

<b>Extent of Cavity Involved</b>	<1/3	1/3 - 2/3	>2/3
	1	2	4
<b>Type of Adhesions</b>	Filmy	Filmy & Dense	Dense
	1	2	4
<b>Menstrual Pattern</b>	Normal	Hypomenorrhea	Amenorrhea
	0	2	4

# **Inclusion criteria**

- **randomized clinical trial**
- **Moderate-severe IUA**
  - **AFS score(American Fertility Society)  $\geq 5$**
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# **Exclusion criteria**

- **quasi-randomized trials**
- **trials without randomization**
- **Not adhesiolysis**

# **Primary outcome**

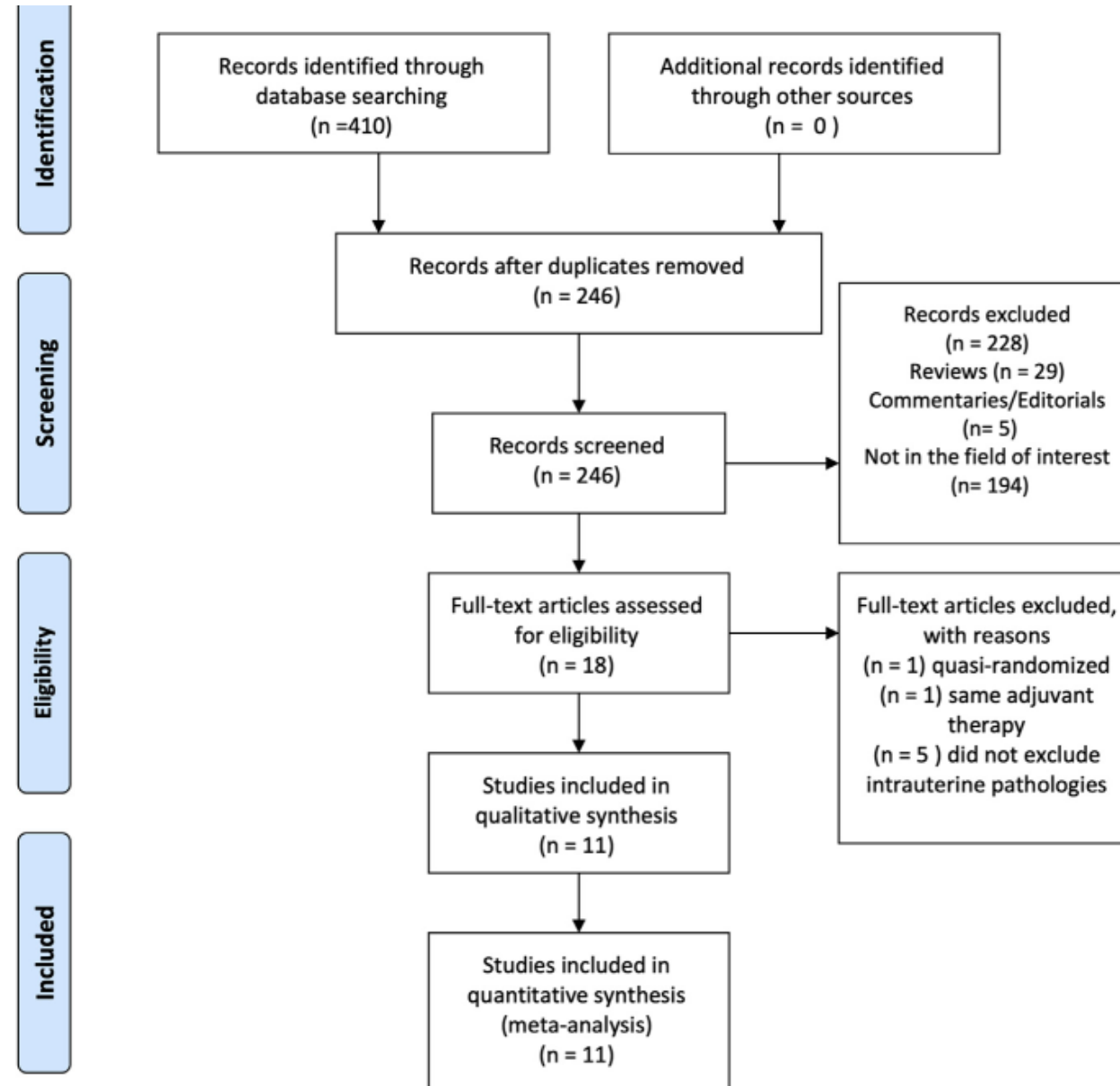
- **IUA recurrence incidence**  
(diagnosed with IUA at f/u diagnostic hysteroscopy)

# **Secondary outcomes**

- **Recurrence the mean adhesion score(AFS)**
- **IUA severity rate(AFS  $\geq$  5)**
- **menstrual pattern changes**
- **clinical pregnancy rate(CPR)**
- **live birth rate**

# Study selection

**FIGURE 1**  
Flow-diagram of the included studies in systematic review and network meta-analysis



# Table 1

**TABLE 1**  
Main characteristics of trials included in the network meta-analysis

Study	Design	Location	Intervention 1	Intervention 2	Intervention 3	Hysteroscope	Type of surgery	Age	Follow-up	Primary outcome	Secondary outcome	IUA recurrence in no treatment arm (%)
Acunzo <sup>15</sup>	RCT single	Italy	Auto-cross-linked Hyaluronic acid	No treatment	-	26Fr rigid resectoscope	IUA	30.5	3 months	IUA recurrence rate	Mean adhesion score; severe IUA rate	13/42 (30.9)
Amer <sup>22</sup>	RCT double	Egypt	Intrauterine balloon	Fresh amnion	Dried amnion	5Fr rigid hysteroscope	IUA	30.4	28 months	Mean adhesion score	IUA recurrence rate; severe IUA rate; CPR	-
Gan <sup>14</sup>	RCT double	China	Dried Amnion	Intrauterine balloon	-	26Fr rigid resectoscope	IUA	30.2	3 months	Mean adhesion score	Changes in menstrual pattern; IUA recurrence rate; CPR; severe IUA rate	16/40 (40.0)
Lin <sup>12</sup>	RCT single	China	Intrauterine balloon	Copper IUD	-	5Fr rigid hysteroscope	IUA	29.9	1 month	IUA recurrence rate	Mean adhesion score; severe IUA rate	-
Mao <sup>23</sup>	RCT double	China	Auto-cross-linked hyaluronic acid	No treatment	-	5Fr rigid hysteroscope	IUA	36.3	6 months	Mean adhesion score	CPR; IUA recurrence rate; severe IUA rate	3/32 (9.3)
Shi <sup>13</sup>	RCT single	China	Intrauterine balloon	No treatment	-	26Fr rigid resectoscope	IUA	32.0	12 months	IUA recurrence rate	Severe IUA rate; changes in menstrual pattern	39/97 (40.2)
Zhou <sup>26</sup>	RCT double	China	Auto-cross-linked hyaluronic acid	Intrauterine balloon	-	26Fr rigid resectoscope	IUA	31.9	3 months	IUA recurrence rate	Mean adhesion score; severe IUA rate	-
Wang <sup>24</sup>	RCT double	China	Dried Amnion	Intrauterine balloon	-	26Fr rigid resectoscope	IUA	31.1	3 months	IUA recurrence rate	Mean adhesion score; severe IUA rate; changes in menstrual pattern	-
Xiao <sup>25</sup>	RCT double	China	Auto-cross-linked hyaluronic acid	Intrauterine balloon	-	26Fr rigid resectoscope	IUA	30.9	3 months	IUA recurrence rate	Mean adhesion score; severe IUA rate	-

(continued)

# Table 1

**TABLE 1**  
**Main characteristics of trials included in the network meta-analysis** *(continued)*

Study	Design	Location	Intervention 1	Intervention 2	Intervention 3	Hysteroscope	Type of surgery	Age	Follow-up	Primary outcome	Secondary outcome	IUA recurrence in no treatment arm (%)
Wang <sup>28</sup>	RCT double	China	Auto-cross-linked hyaluronic acid	AC+IUD	IUD	5Fr rigid hysteroscope	IUA	32.1	1 month	IUA recurrence rate	Mean adhesion score; severe IUA rate	-
Huang <sup>27</sup>	RCT double	China	Intrauterine balloon	Intrauterine balloon + IUD	-	5Fr rigid hysteroscope	IUA	31.7	2 months	Mean adhesion score	IUA recurrence rate; CPR	-

*CPR*, clinical pregnancy rate; *Fr*, French; *IUA*, intrauterine adhesions; *IUD*, intrauterine device; *RCT*, randomized controlled trials.

# Table 1

## Hysteroscopic adhesiolysis

- **8 mm rigid hysteroscope: 6(studies)**
- **4 mm office hysteroscope: 5**
  
- **monopolar energy: 3**
- **bipolar energy: 4**
- **scissors: 2**
- **not report: 2**



# Table 1

## Mechanical antiadhesion treatment

- **HAG**
- **intrauterine balloon(± amnion graft)**
- **IUD**
- **IUD+balloon**
- **HAG+balloon**
- **Placebo(No treatment)**
  
- **Postoperative hormonal treatment: 7 studies**
  - 4 estrogen+progesterone for 2 or 3 cycles
  - 3 estrogen-only for 2 cycles
  - follow-up: 30 days to 28 months

# Table 1

## Types of strategies

- HAG
- intrauterine balloon( $\pm$ frozen amnion graft)
- IUD
- IUD+balloon
- HAG+ballon
- Palcebo(No treatment)
  
- **Postoperative hormonal treatment: 7 studies**
  - **4 estrogen+progesterone for 2 or 3 cycles**
  - **3 estrogen-only for 2 cycles**
  - **2<sup>nd</sup> look hysteroscopy : 30 days to 28 months**

# Table 2

**TABLE 2**  
Inclusion and exclusion criteria of included studies

Study	Inclusion criteria	Exclusion criteria	Surgical approach
Acunzo <sup>15</sup>	Hysteroscopic diagnosis of intrauterine adhesions	Age over 50 years, weight over 100 kg, menopause or pregnancy, uterovaginal prolapse and severe urinary symptoms, malignancy, severe intercurrent pathology, presence of other intrauterine lesions (ie, polyps, myomas, septa).	Monopolar resection through hook knife
Amer <sup>22</sup>	Women with severe IUAs diagnosed at office hysteroscopy	NA	Monopolar resection through hook knife
Gan <sup>14</sup>	Age <40 years; hypomenorrhea or amenorrhea; infertility or at least one pregnancy loss; AFS IUA score of at least eight.	Premature menopause; presence of other intrauterine lesions (eg, polyps, myoma, or septa); and severe intercurrent pathology	Bipolar resection through cutting loop
Lin <sup>12</sup>	Age between 18–40 years; moderate to severe intrauterine adhesion (AFS score over 5); no history of hysteroscopic adhesiolysis; written consent obtained; agreement to have second-look hysteroscopy.	Minimal adhesion (AFS score <5) and previous hysteroscopic adhesiolysis.	Monopolar resection through hook knife
Mao <sup>23</sup>	Moderate to severe IUA (AFS score $\geq 5$ ) infertility for at least 1 year; expected to undergo IVF/ICSI and FET; and had at least one good quality embryo left	Uterine malformations, endometrial diseases, endometriosis, and adenomyosis	Mechanical removal using 5Fr blunt scissors
Shi <sup>13</sup>	Women aged 18–40 years with moderate to severe intrauterine adhesion	Minimal intrauterine adhesions	Bipolar energy adhesiolysis
Zhou <sup>26</sup>	Women aged 20–40 years; moderate to severe IUAs (AFS score $\geq 5$ ); written informed consent obtained;	Previous history of endometrial tuberculosis; previous history of uterine artery embolization; patients with significant medical illness.	Bipolar energy adhesiolysis
Wang <sup>24</sup>	Infertile women with moderate and severe IUA (AFS score $\geq 5$ );	NA	NA
Xiao <sup>25</sup>	Patients with moderate to severe IUA (AFS score $\geq 5$ );	NA	NA
Wang <sup>28</sup>	Infertile women aged 20–44 with mild-to-severe IUA	Surgical contraindications, patients with contraindications for postoperative hormone replacement therapy, patients with fibroids and uterus anomalies, or patients who were allergic to treatment	Bipolar electrosurgical removal of adhesions
Huang <sup>27</sup>	Age between 18–45 years, no previous hysteroscopic adhesiolysis, willingness to undergo a second-look hysteroscopy, moderate to severe IUA according to the AFS scoring system (AFS score $\geq 5$ )	Presence of other intrauterine pathology (ie, myoma or septum); premature menopause and severe intercurrent disease,	Mechanical removal using 5Fr blunt scissors

AFS, American Fertility Society; FET, frozen embryo transfer; ICSI, intra-cytoplasmic sperm injection; IUA, intrauterine adhesions; IVF, in-vitro fertilization; NA: not available.

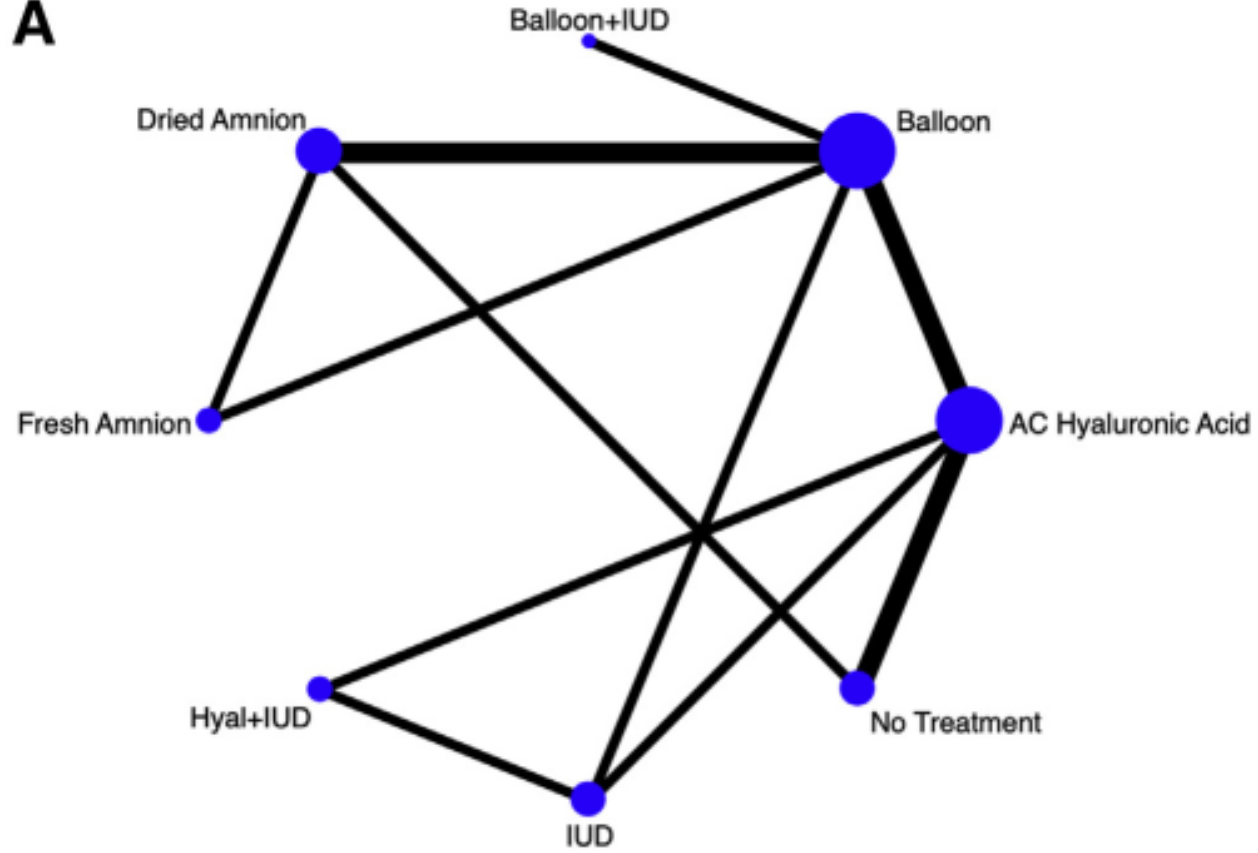
2-4.

**Results**



# 1. Intrauterine adhesions recurrence

A

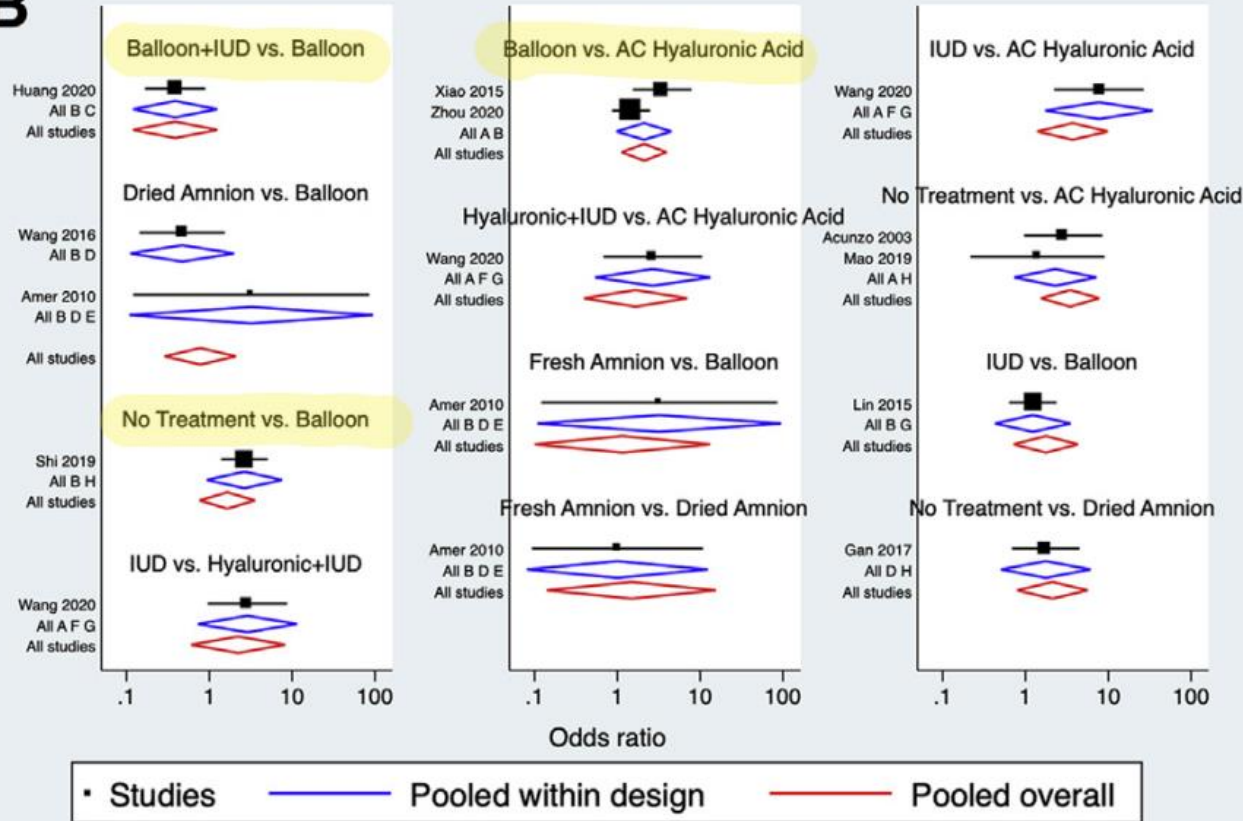


# 1. Intrauterine adhesions recurrence

A

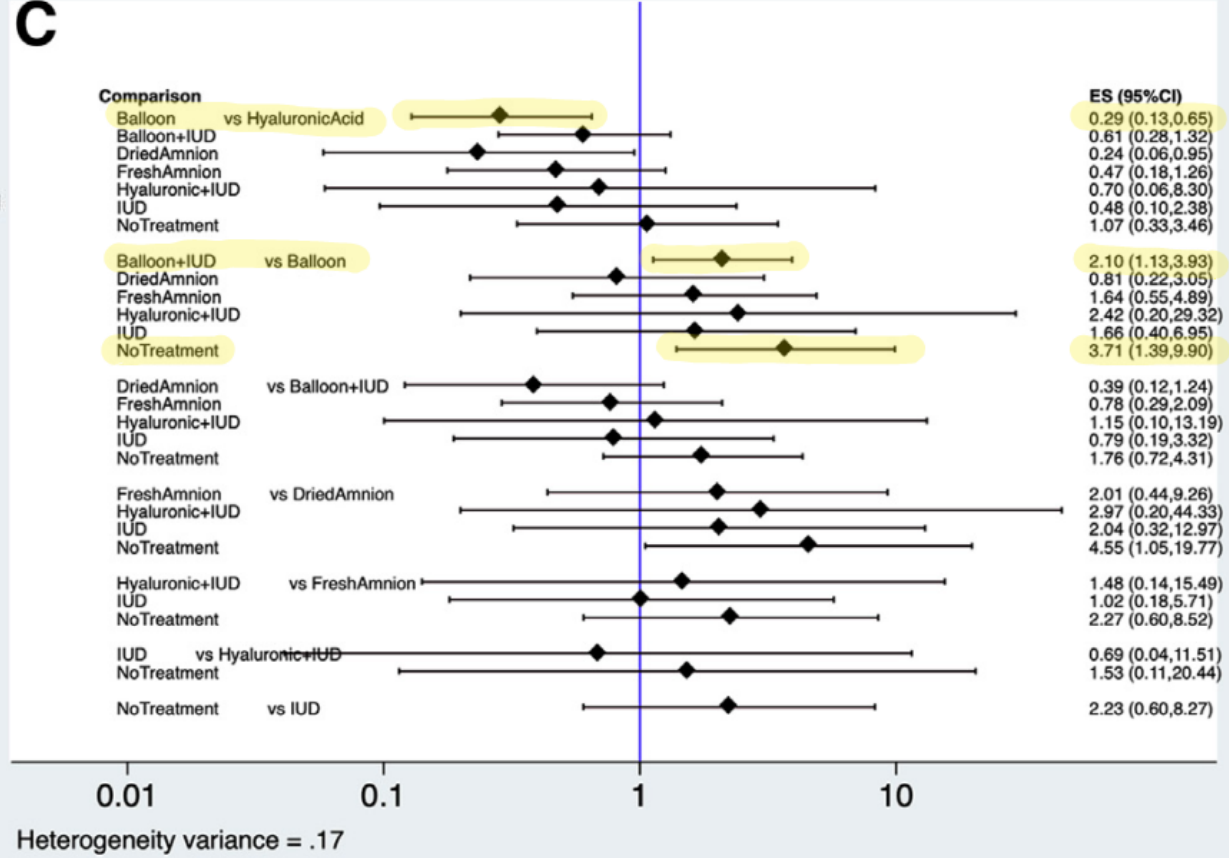
Balloon+IUD

B



Test of consistency:  $\chi^2(4)=3.92, P=0.416$

C



- **HAG勝 vs balloon (RR:0.29)**
- **Balloon vs balloon + IUD勝 (RR:2.10)**
- **No treatment vs balloon勝 (RR:3.71)**

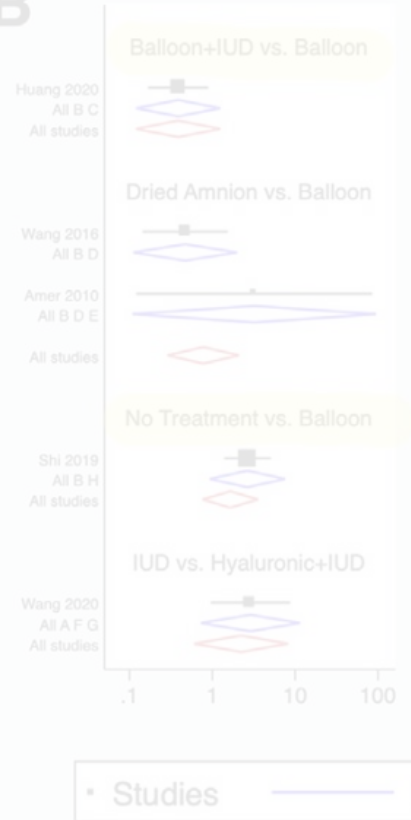
# 1. Intrauterine adhesions recurrence

A

Balloon+IUD

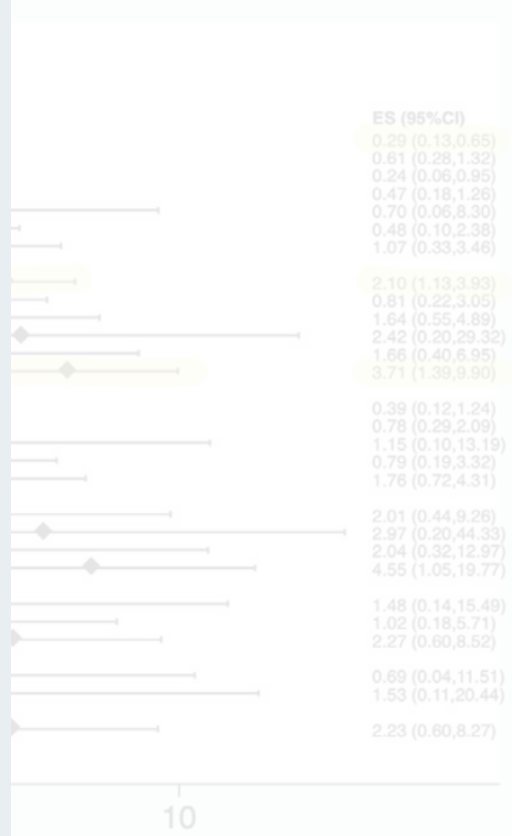
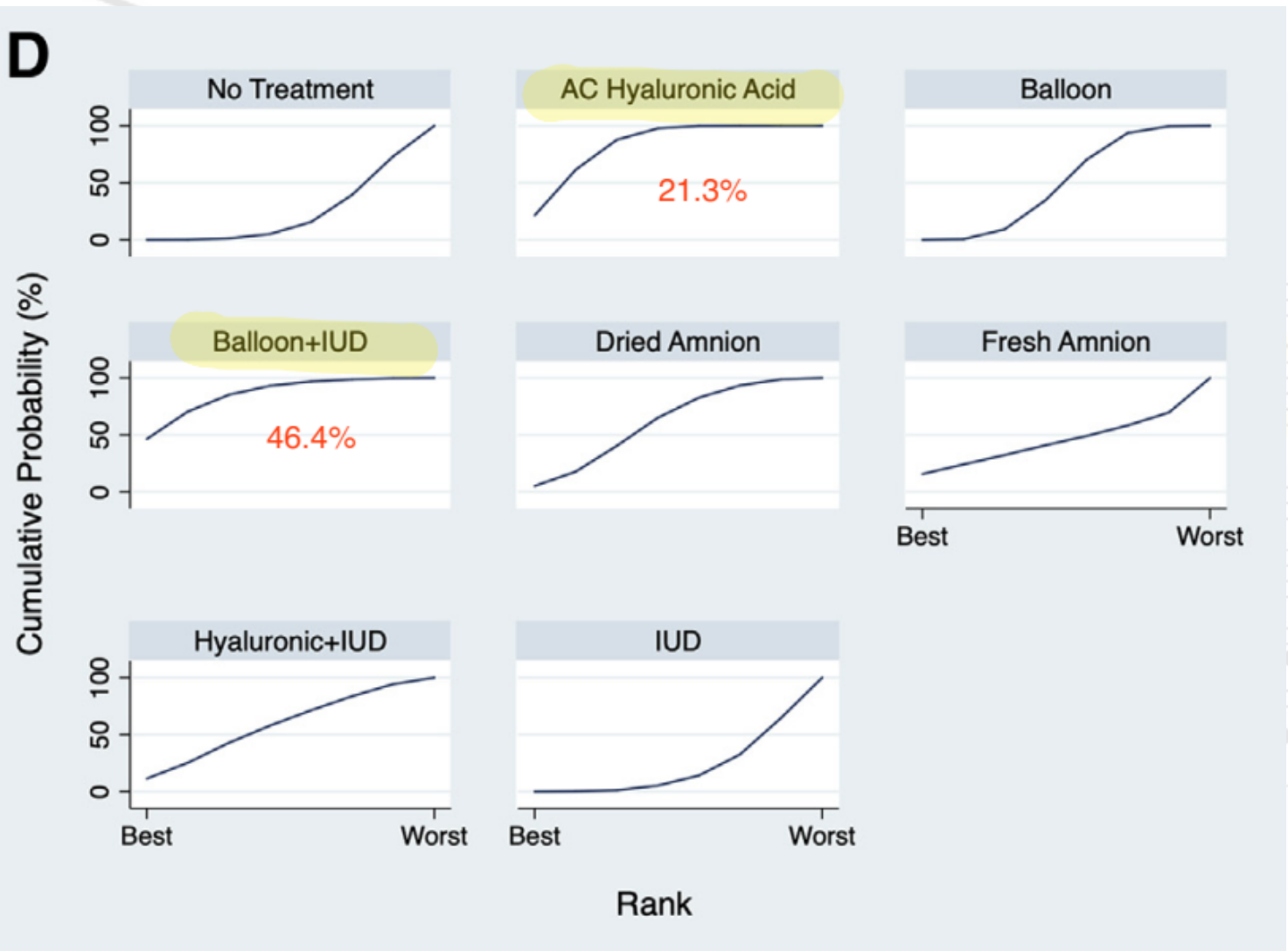
Dried Amnion

B



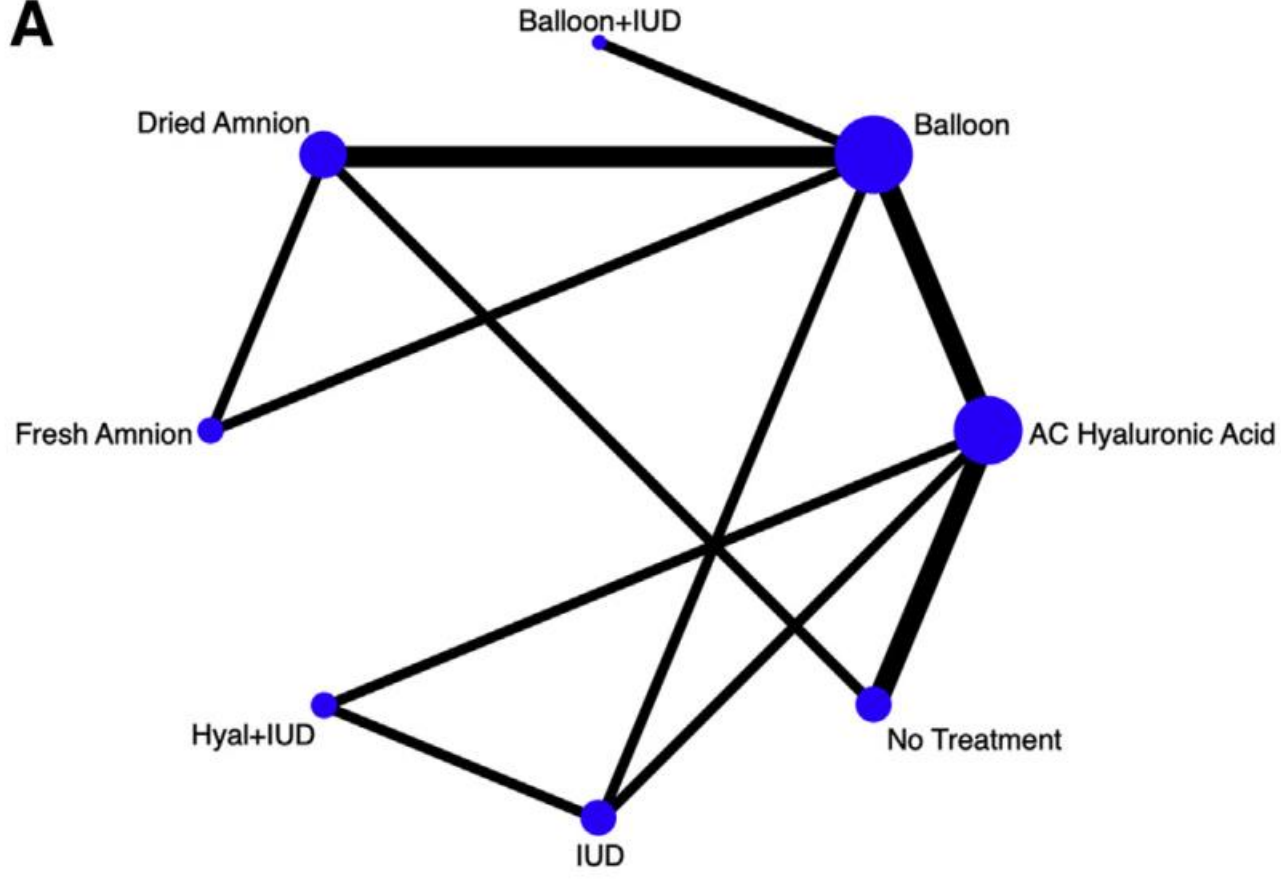
Test of consistency:  $\chi^2(4)=3.92, P=0.416$

D



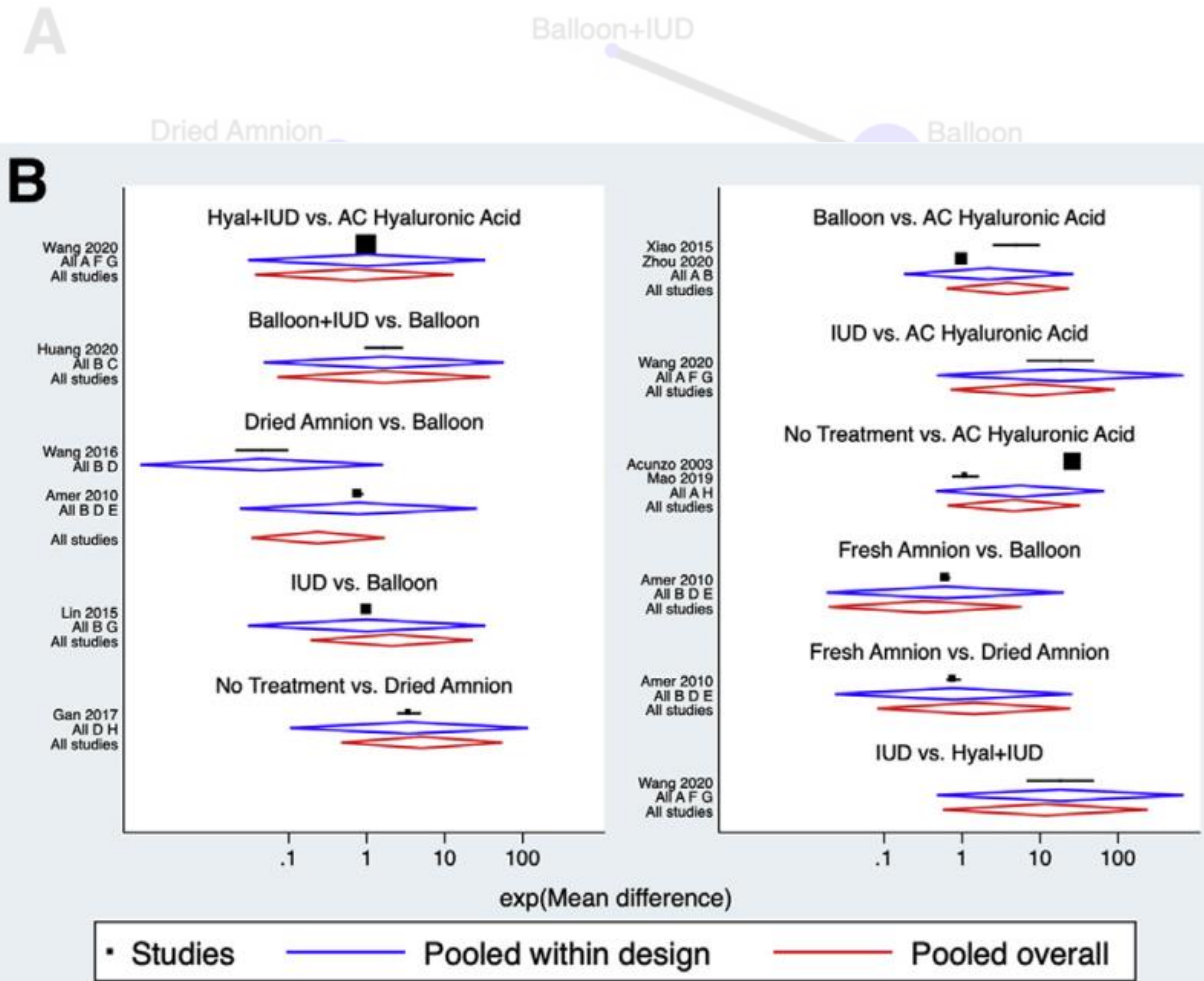
# 2. Mean adhesion score changes

A

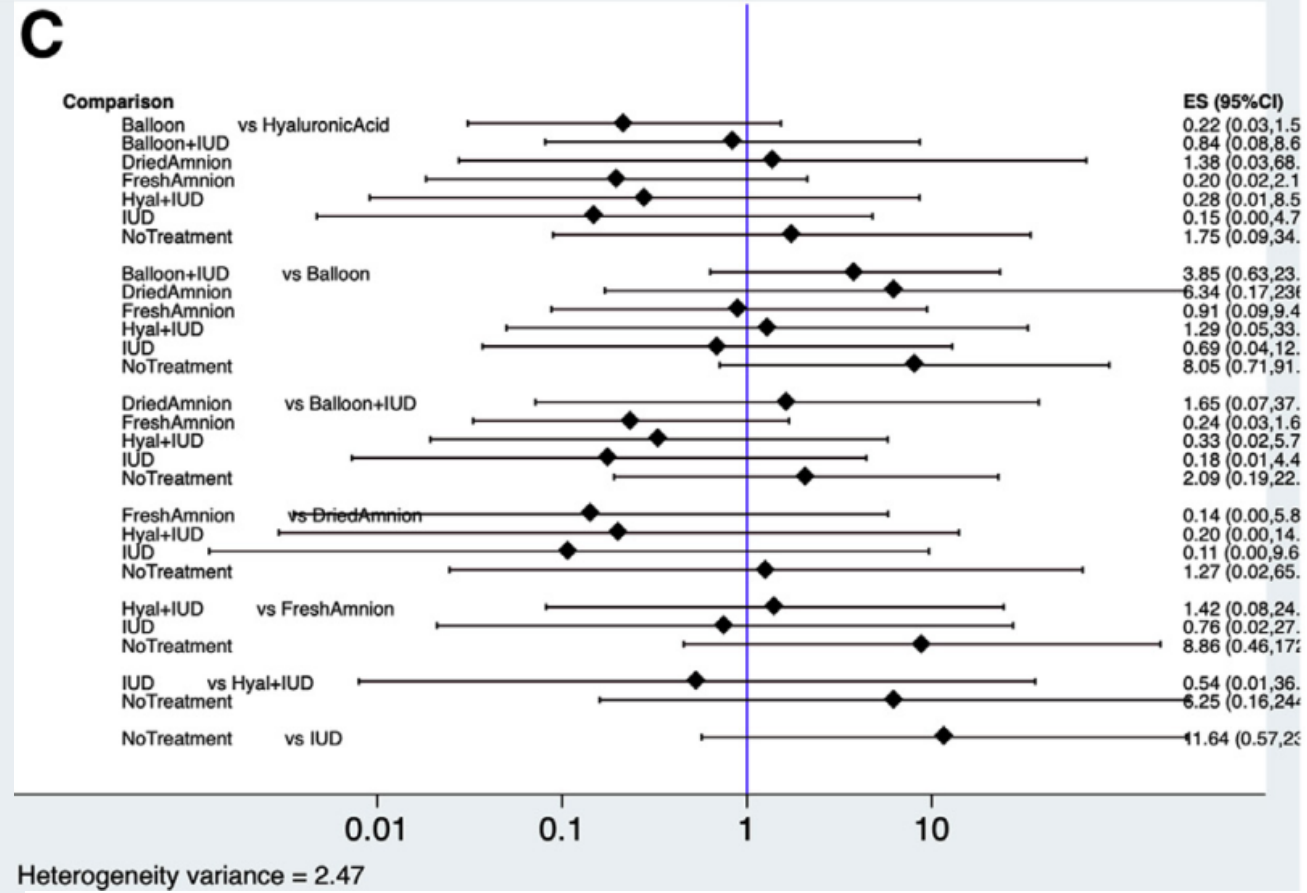




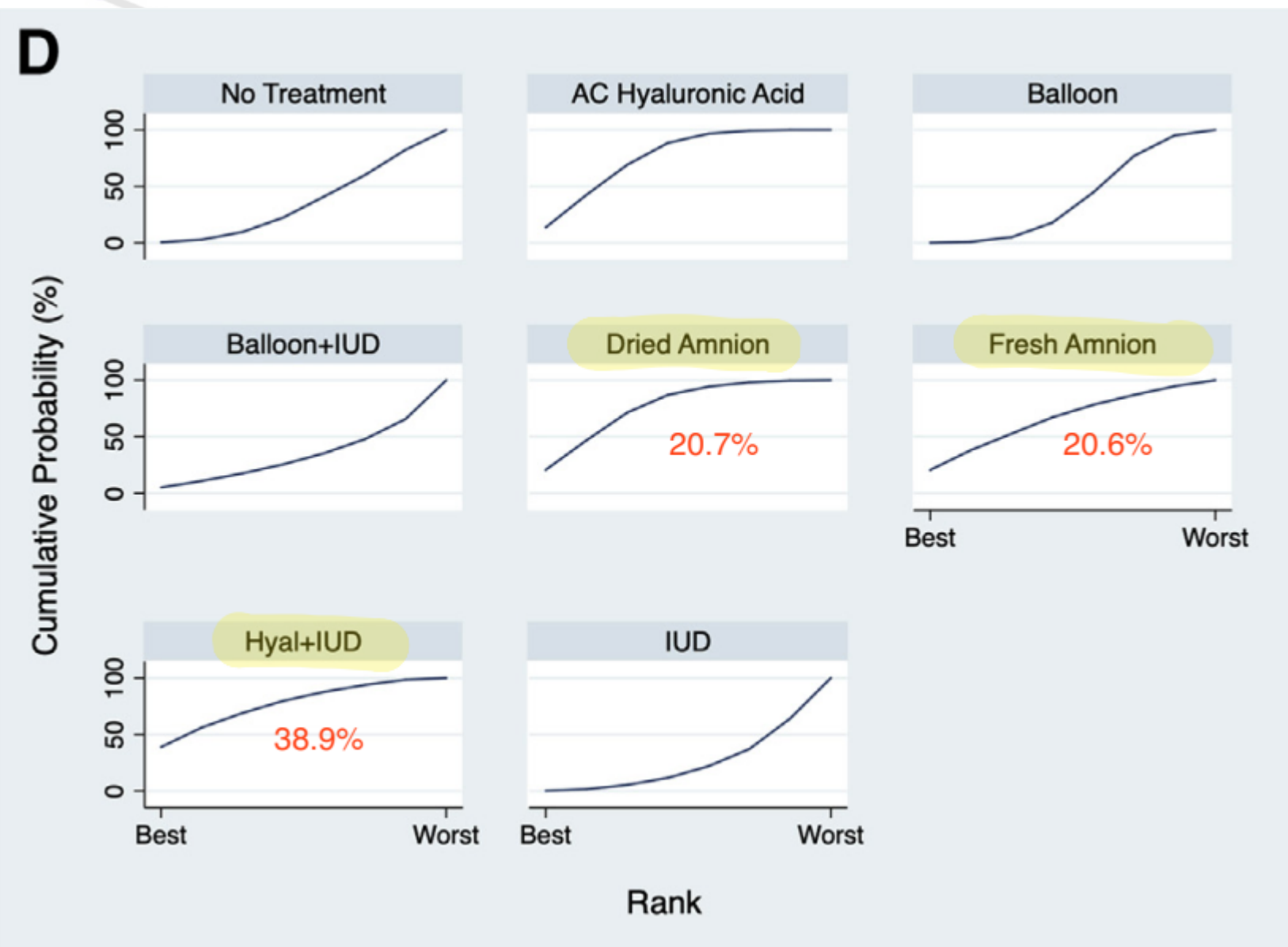
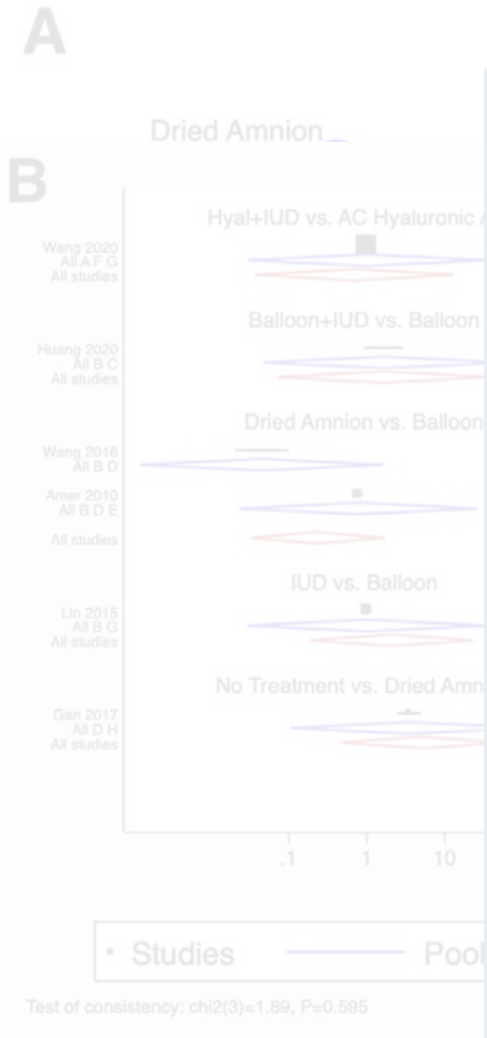
# 2. Mean adhesion score changes



Test of consistency:  $\chi^2(3)=1.89, P=0.595$

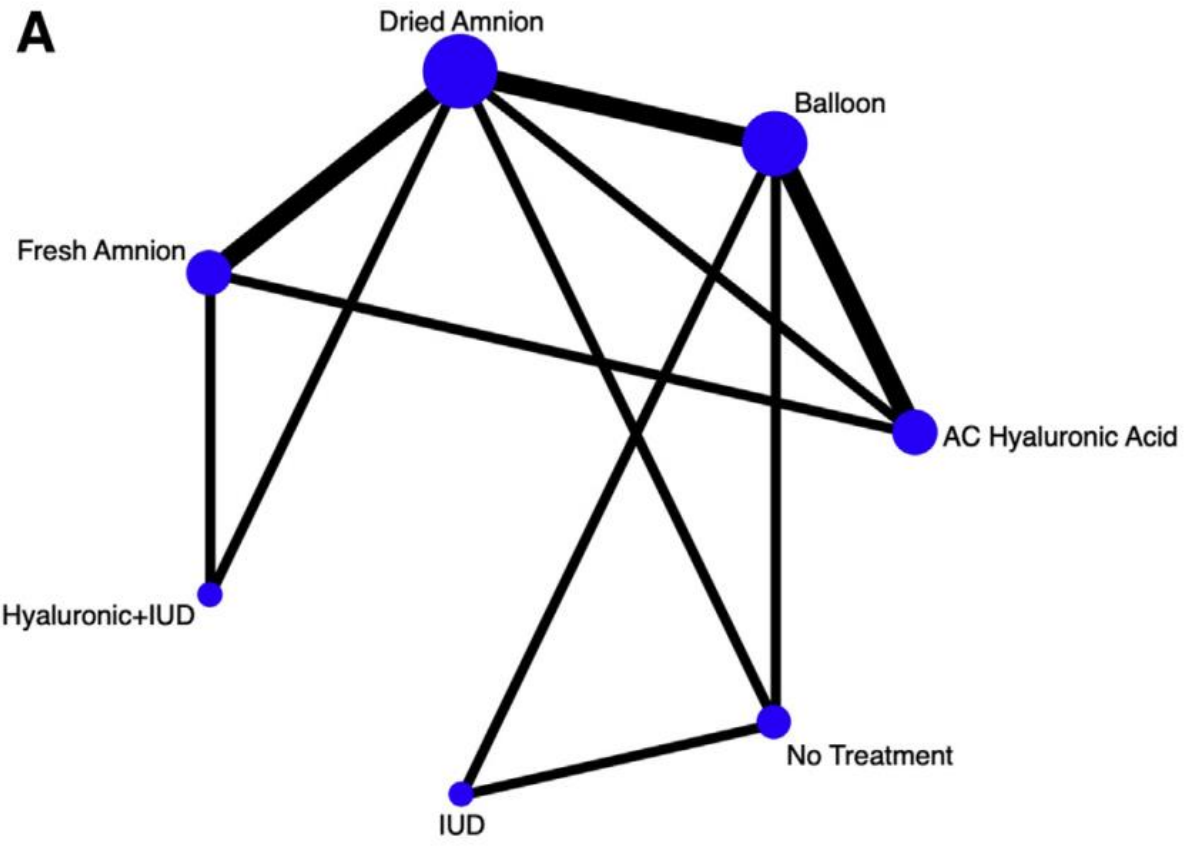


# 2. Mean adhesion score changes



ES (95%CI)
0.22 (0.03, 1.5)
0.84 (0.08, 8.6)
1.38 (0.03, 68)
0.20 (0.02, 2.1)
0.28 (0.01, 8.5)
0.15 (0.00, 4.7)
1.75 (0.09, 34)
3.85 (0.63, 23)
6.34 (0.17, 231)
0.91 (0.09, 9.4)
1.29 (0.05, 33)
0.69 (0.04, 12)
8.05 (0.71, 91)
1.65 (0.07, 37)
0.24 (0.03, 1.6)
0.33 (0.02, 5)
0.18 (0.01, 4.4)
2.09 (0.19, 22)
0.14 (0.00, 5.8)
0.20 (0.00, 14)
0.11 (0.00, 9.6)
1.27 (0.02, 65)
1.42 (0.08, 24)
0.78 (0.02, 27)
8.86 (0.46, 17)
0.54 (0.01, 36)
6.25 (0.16, 24)
11.64 (0.57, 2)

# 3. Intrauterine adhesions severity



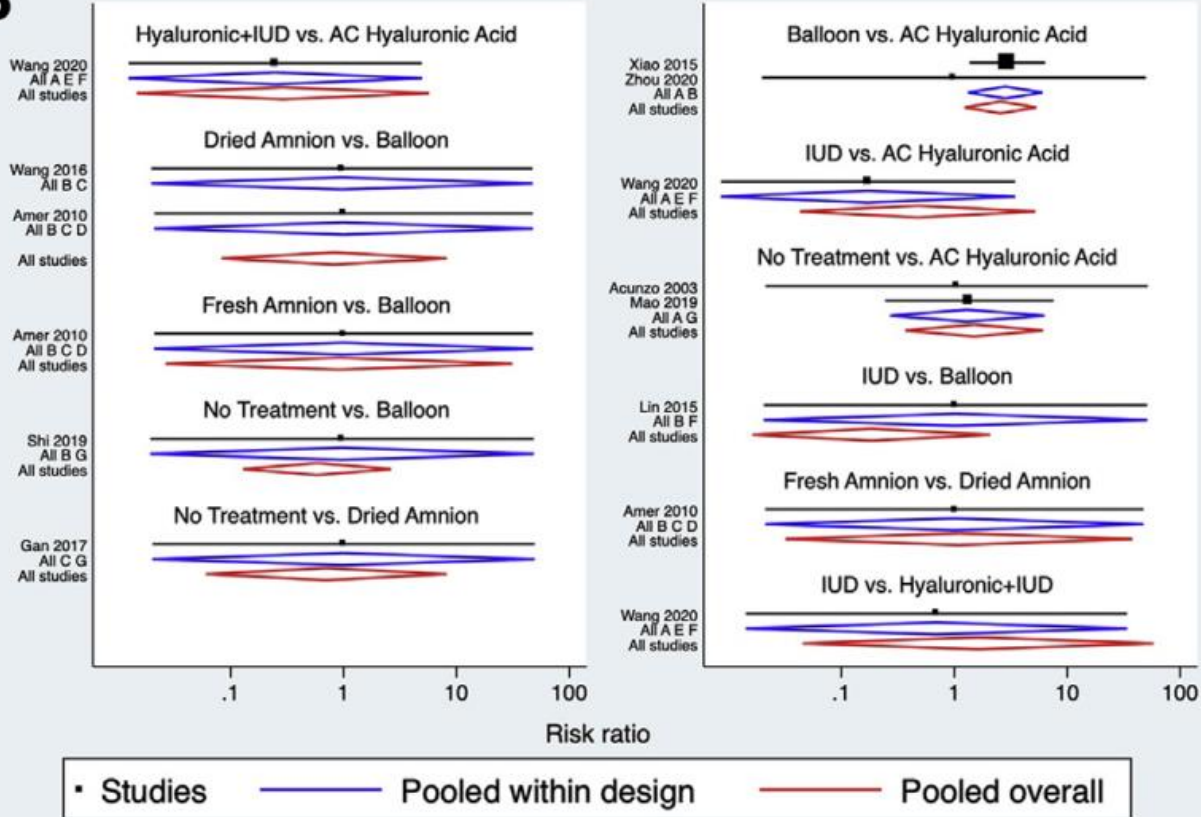
# 3. Intrauterine adhesions severity

A

Dried Amnion

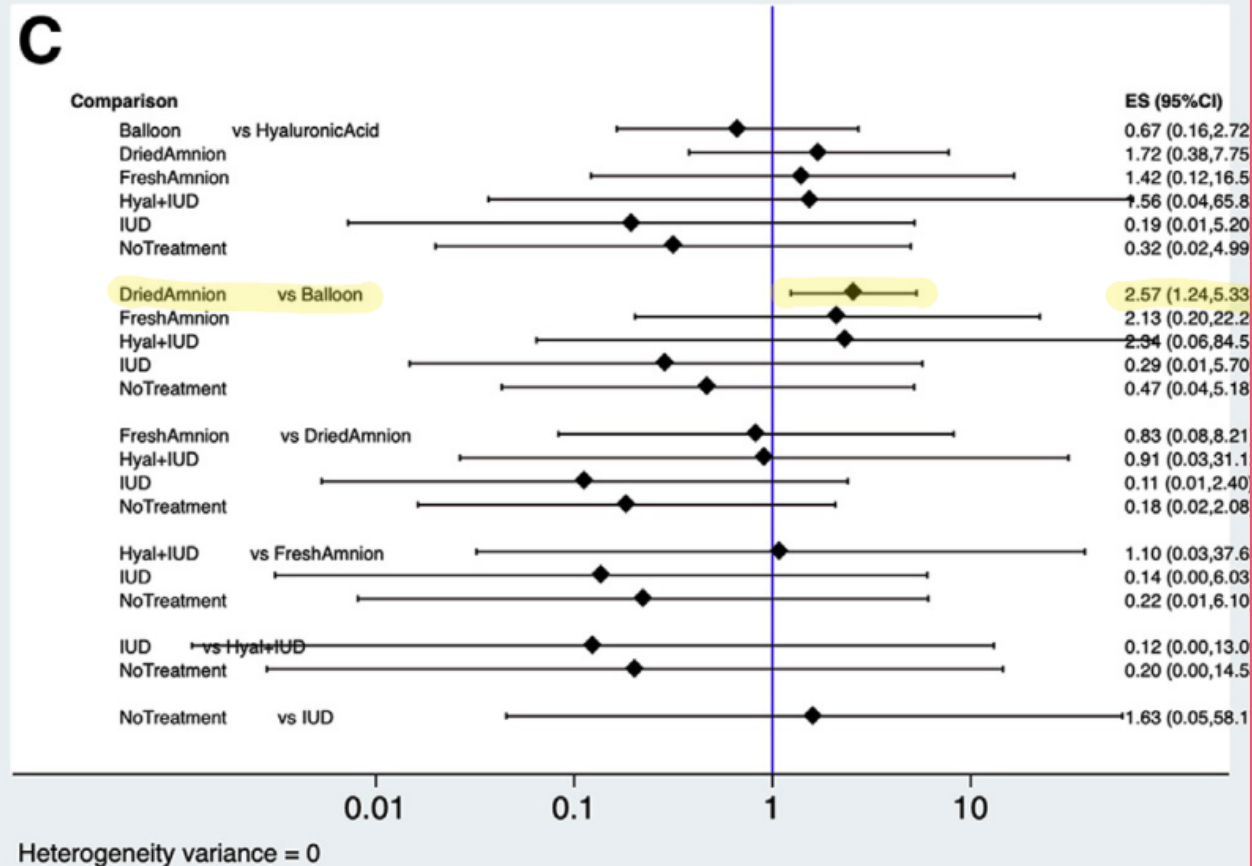
Balloon

B



Test of consistency:  $\chi^2(4)=1.38, P=0.847$

C



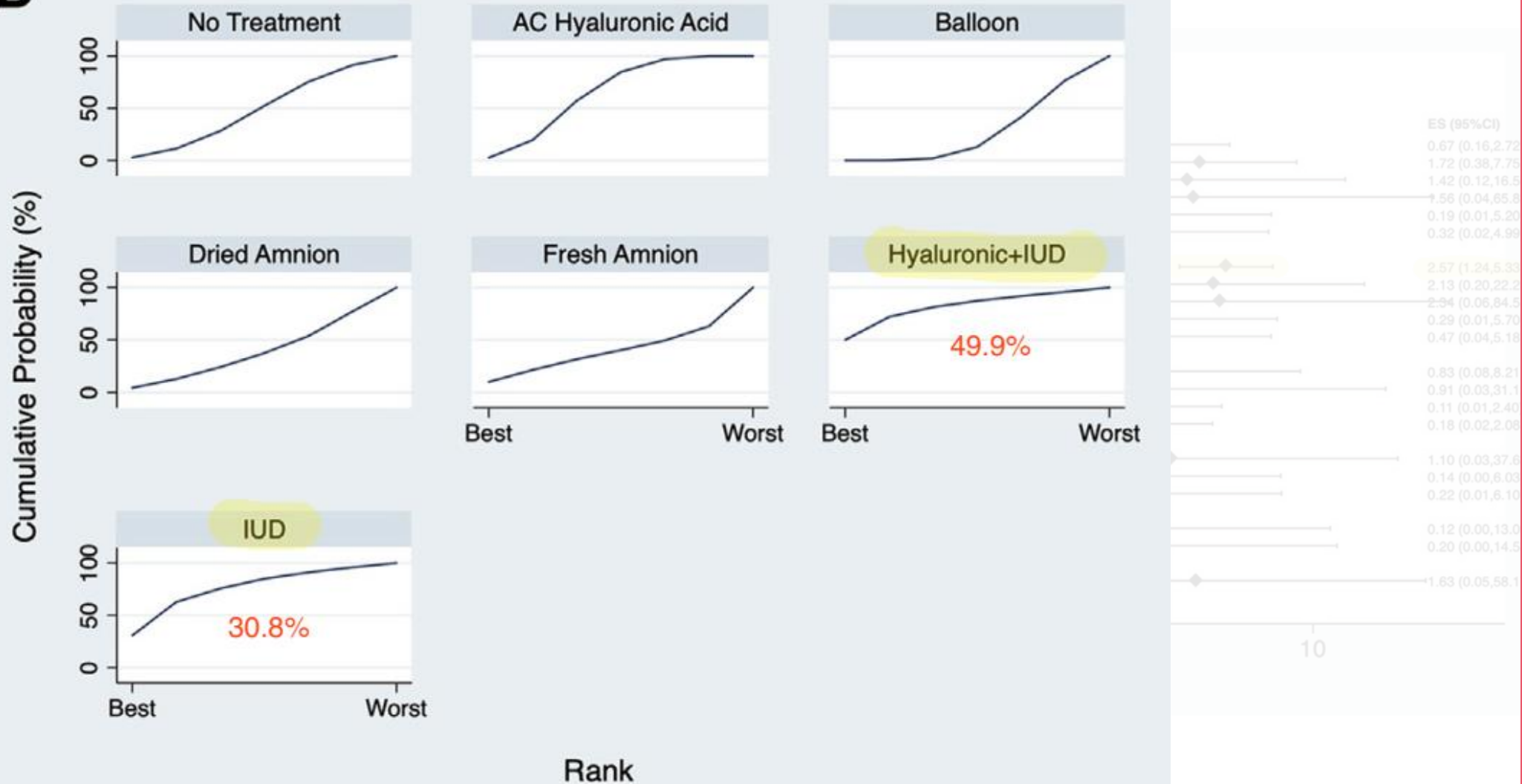
- **Balloon vs dried amnion勝 (RR:2.57)**

# 3. Intrauterine adhesions severity

A

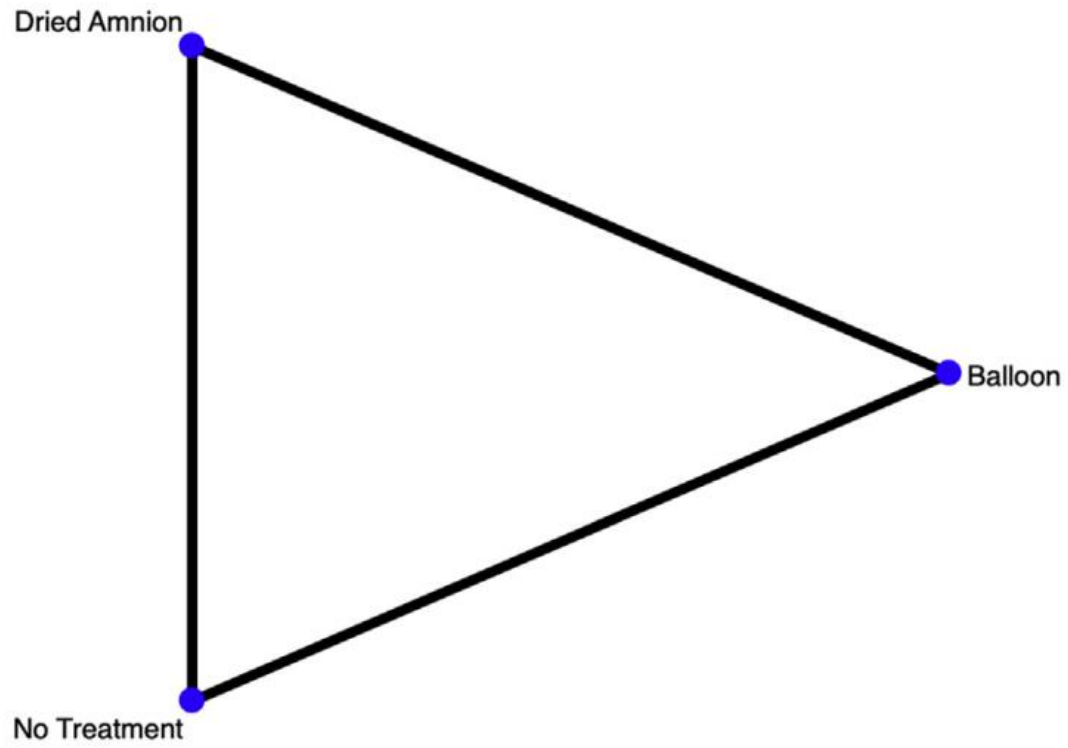


D



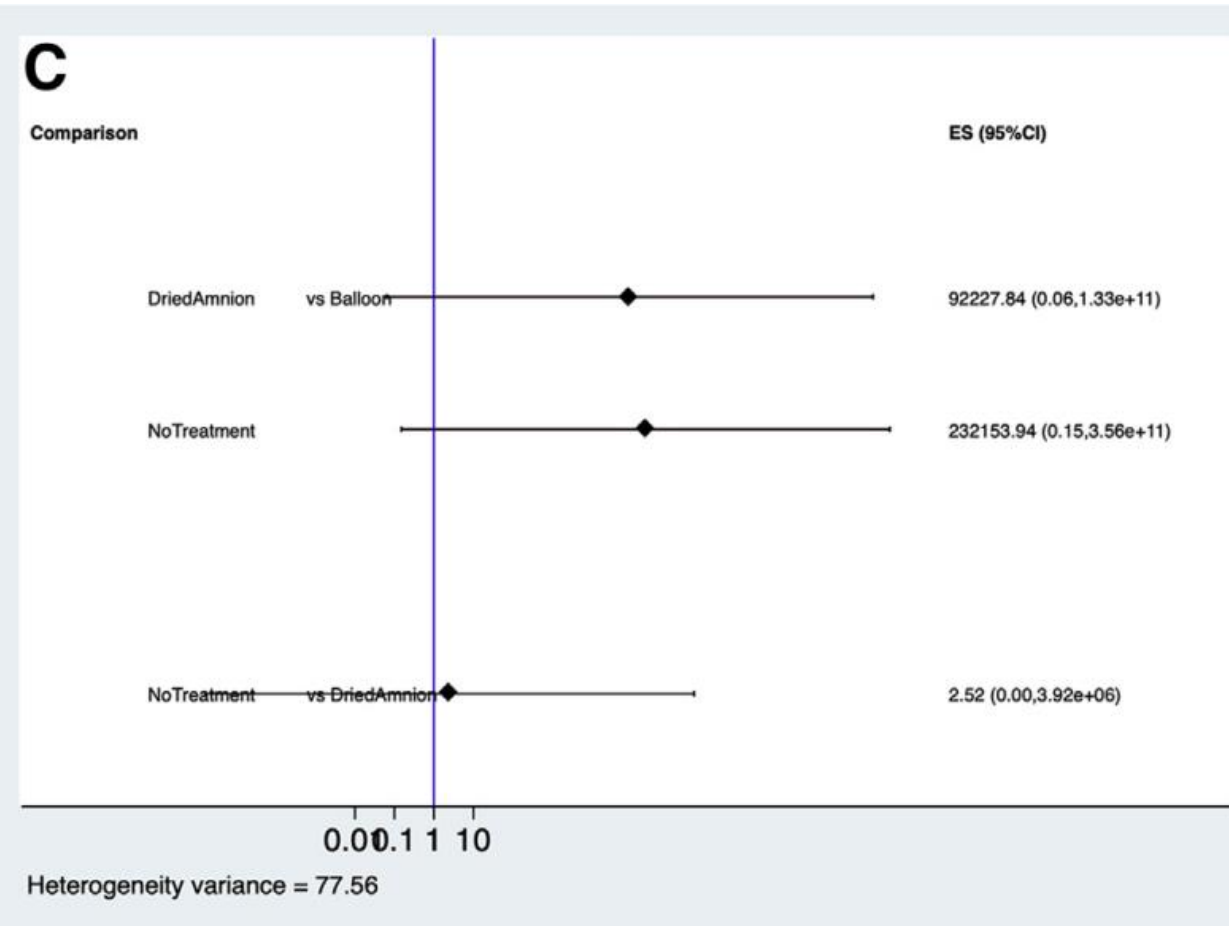
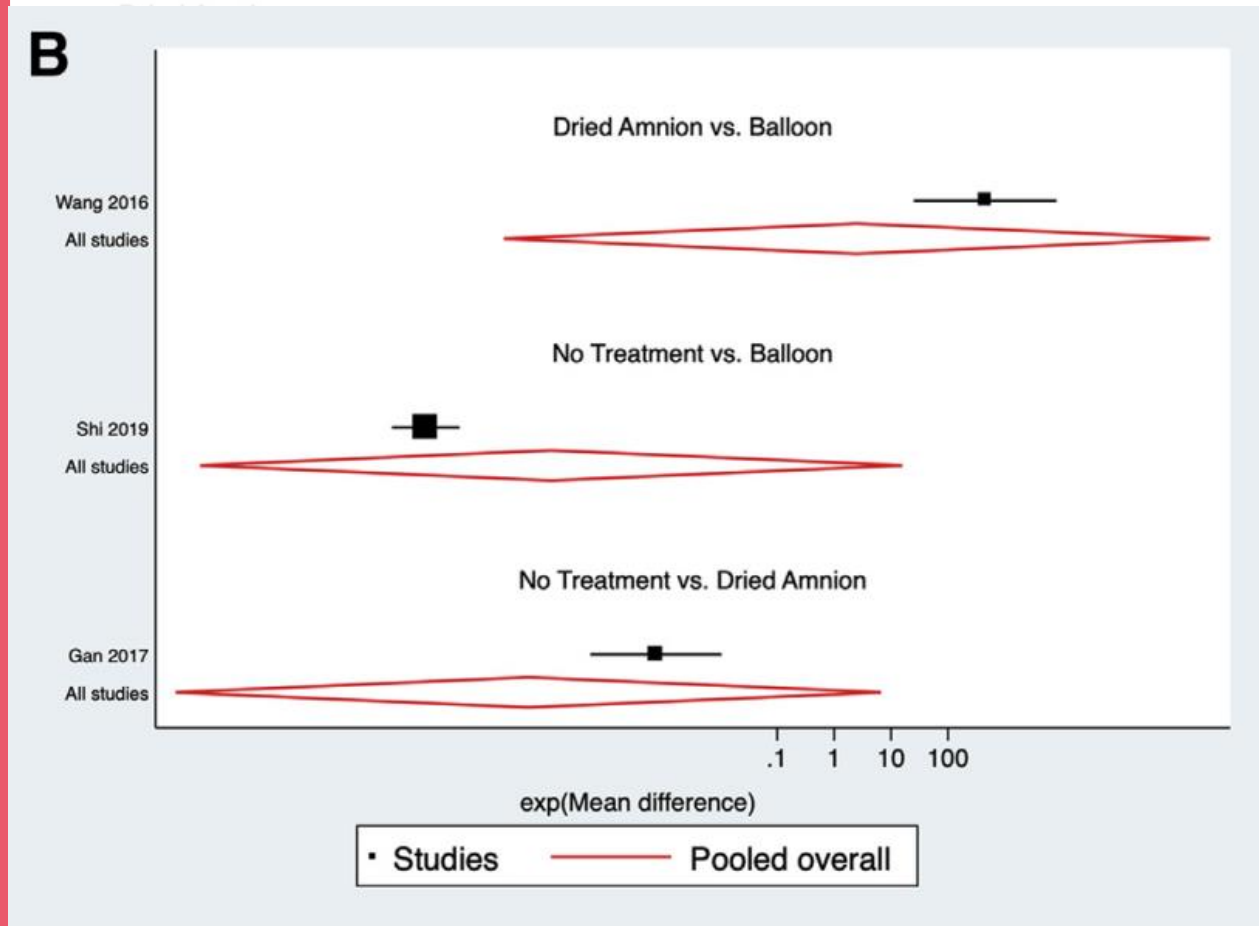
# 4. Changes in menstrual pattern

A



# 4. Changes in menstrual pattern

A

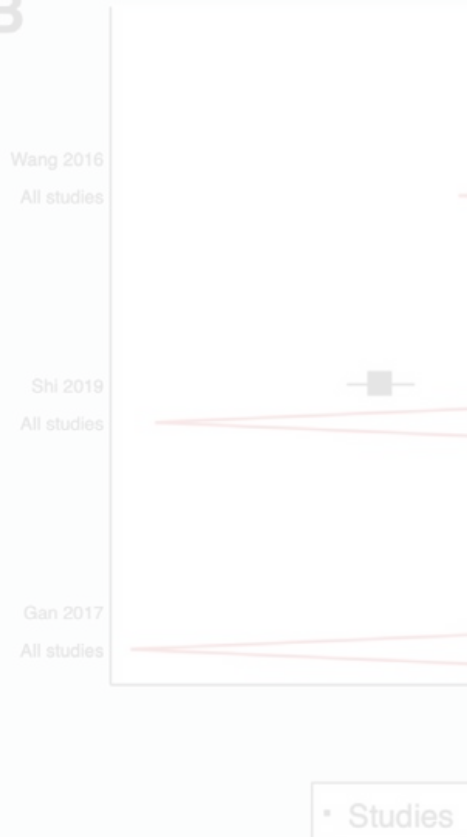




# 4. Changes in menstrual pattern

A

B



D



ES (95%CI)

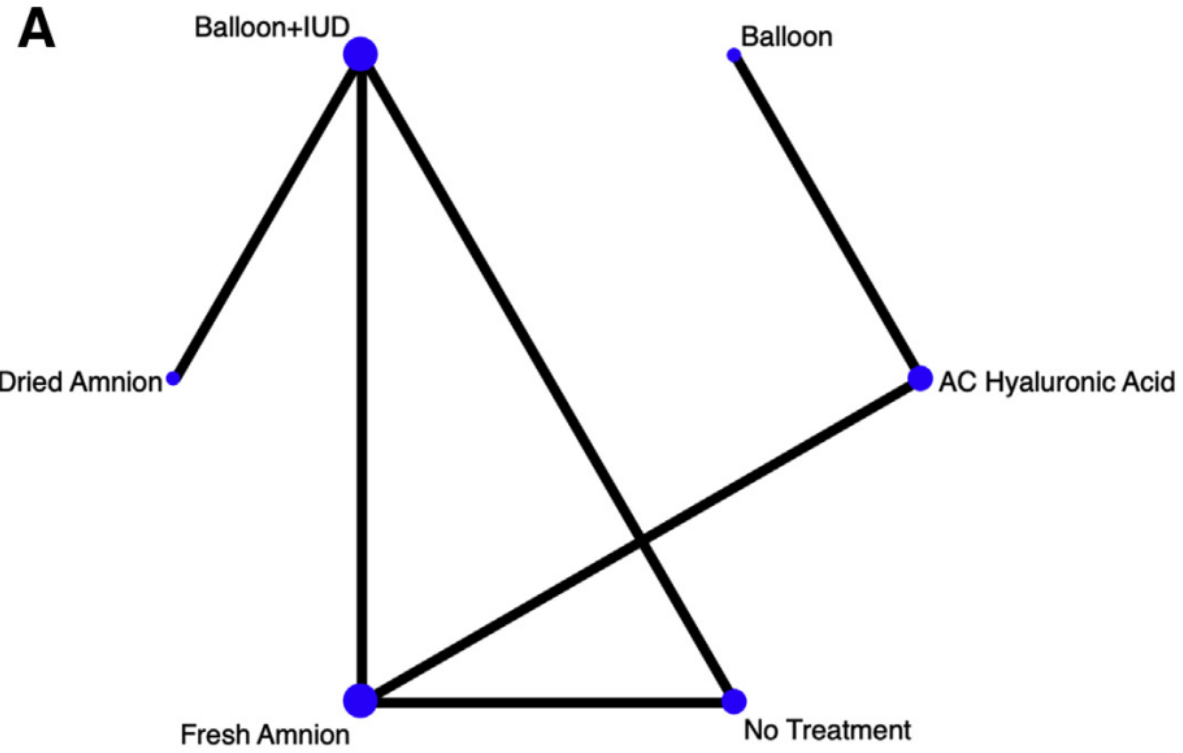
92227.84 (0.06,1.33e+11)

232153.94 (0.15,3.56e+11)

2.52 (0.00,3.92e+06)

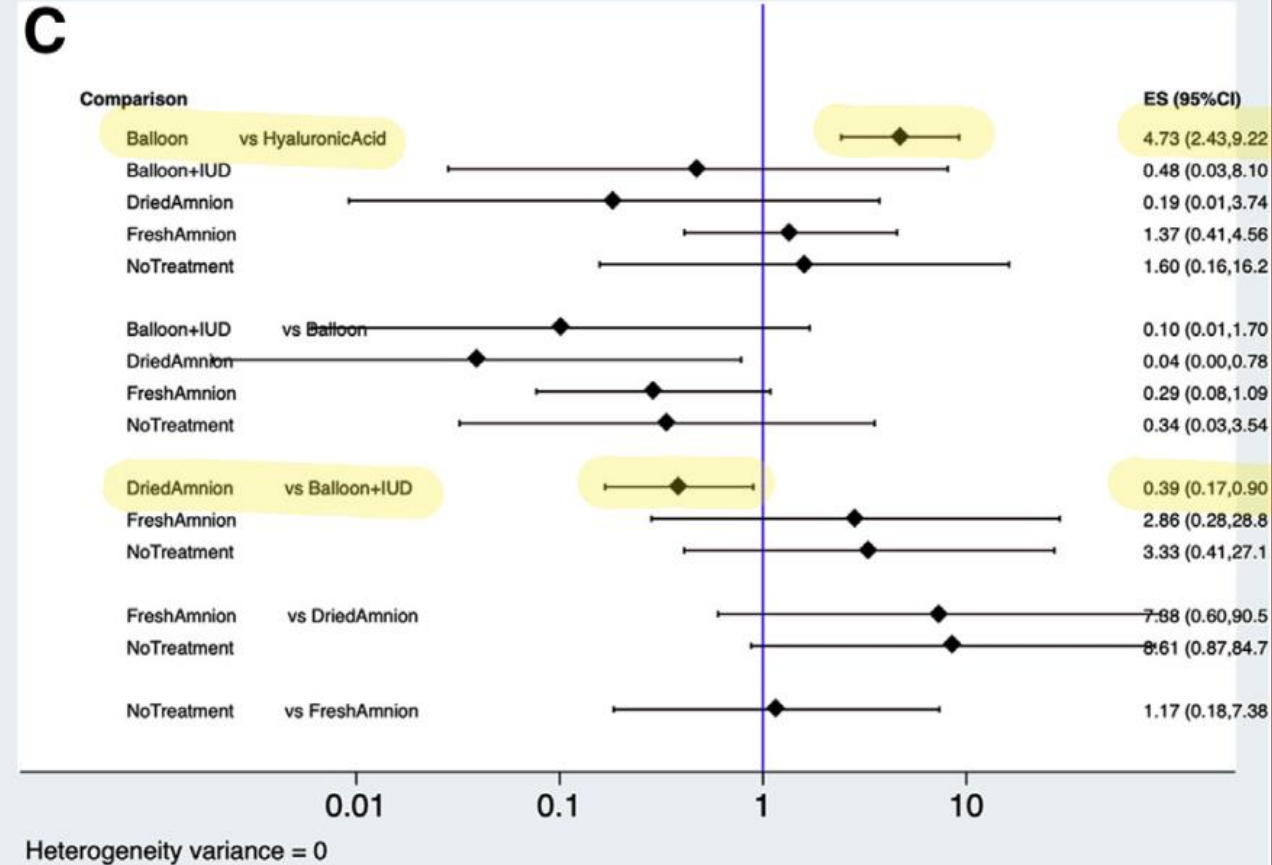
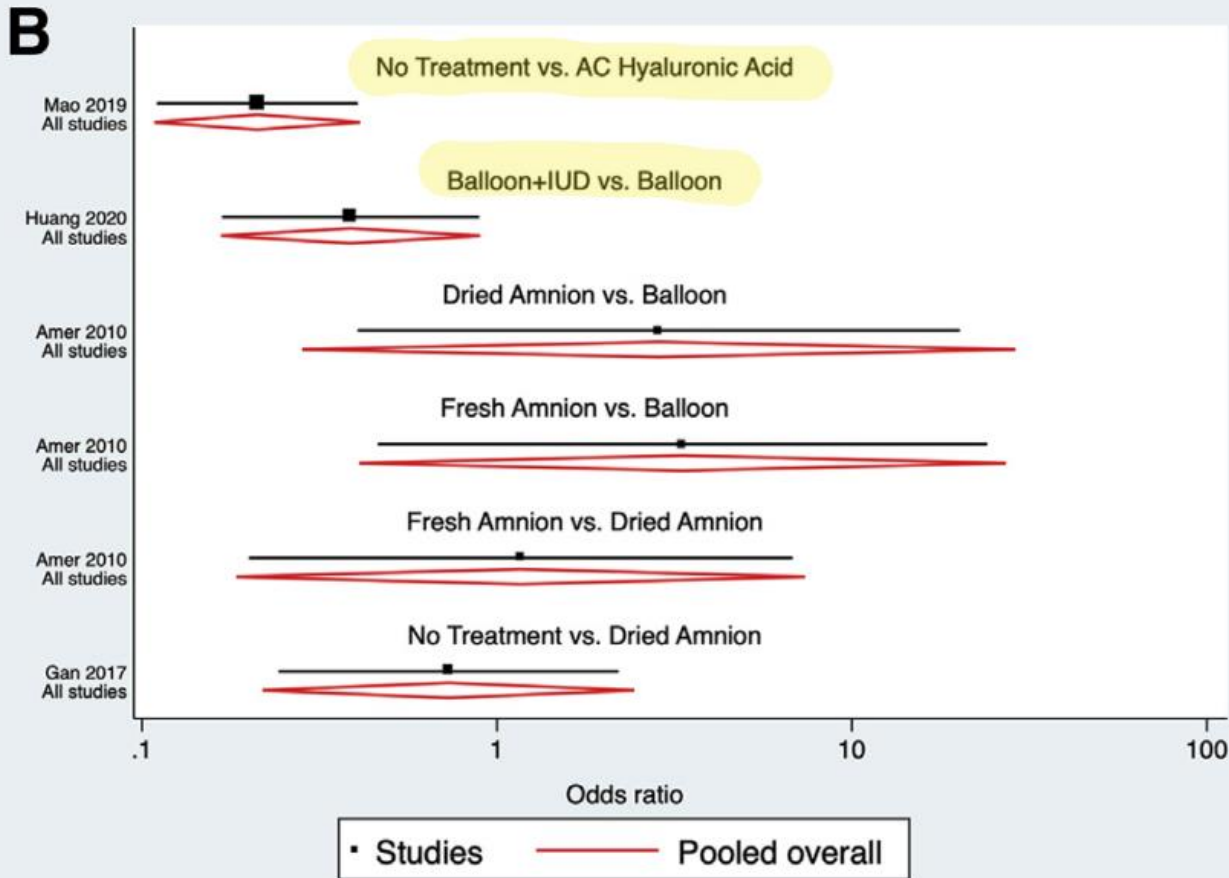


# 5. Clinical pregnancy rate



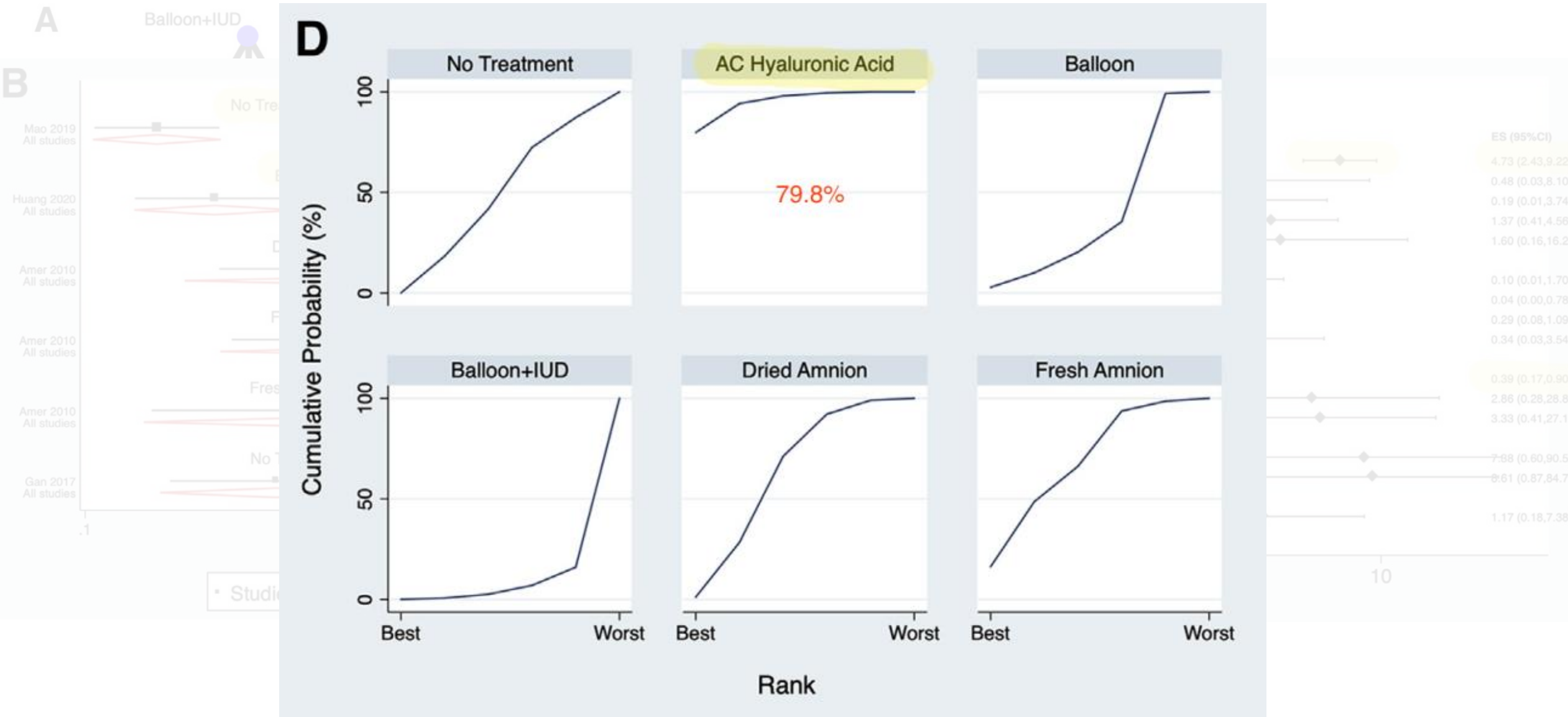
# 5. Clinical pregnancy rate

A Balloon+IUD Balloon



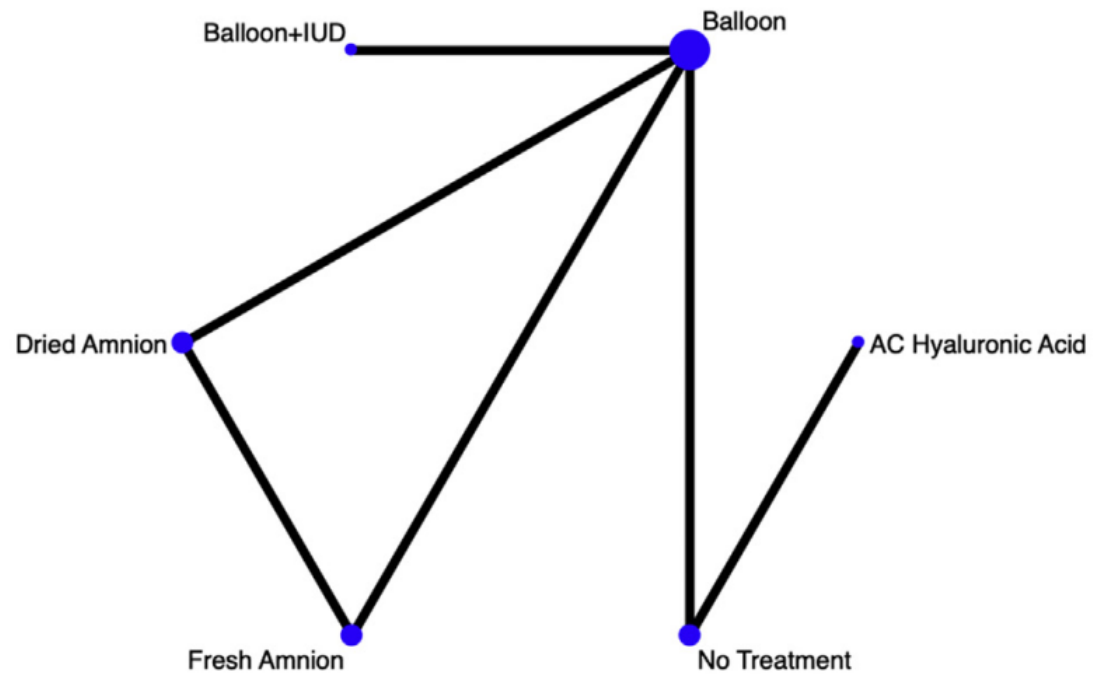
- **HAG勝 vs balloon (OR:4.73)**
- **Balloon + IUD vs dried amnion勝(OR:0.39)**

# 5. Clinical pregnancy rate



# 6. Live birth rate

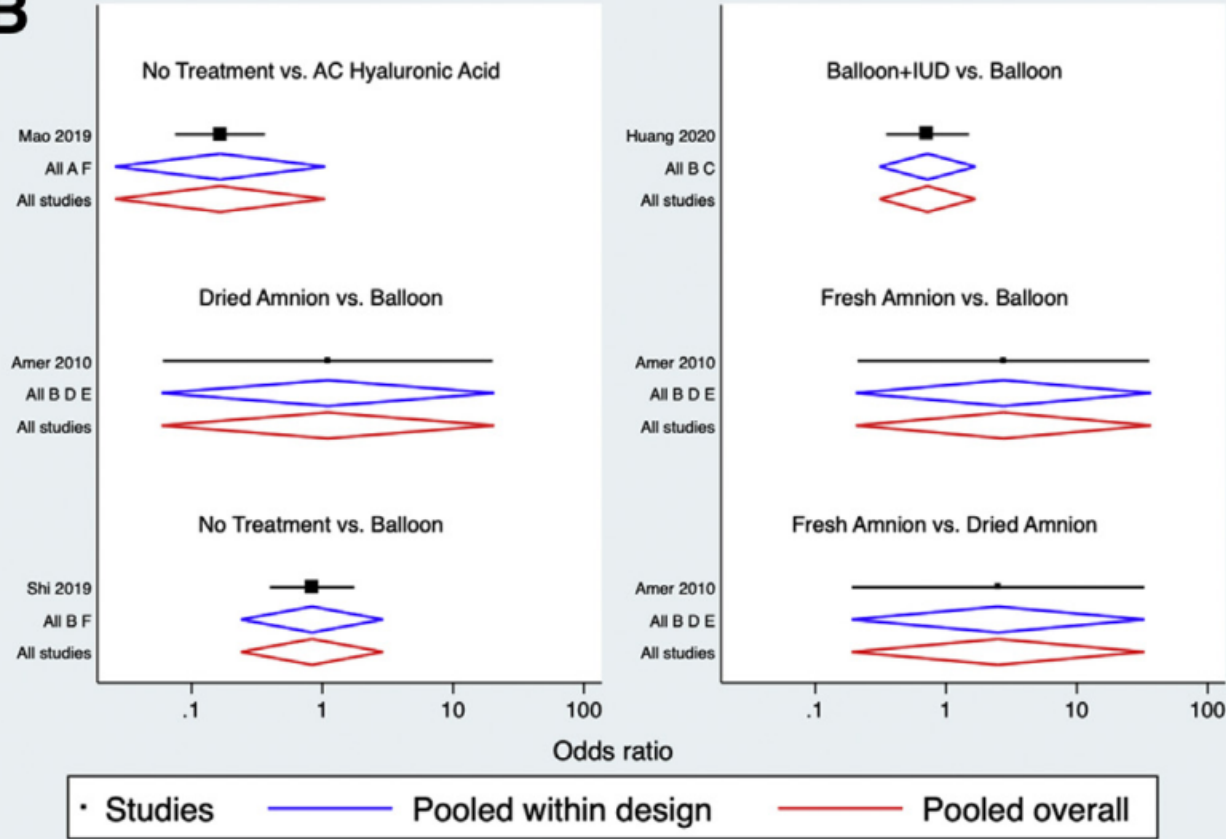
A



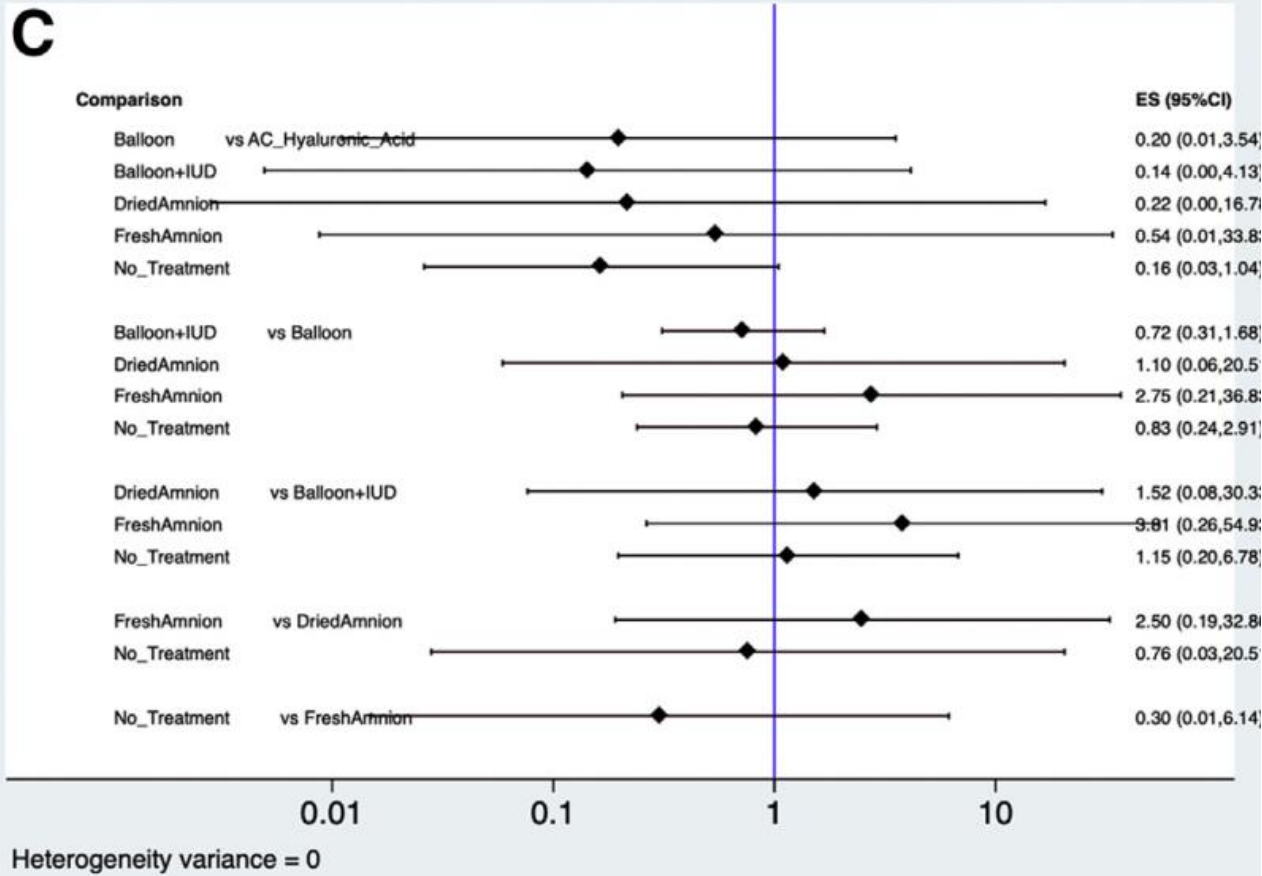
# 6. Live birth rate

A

B

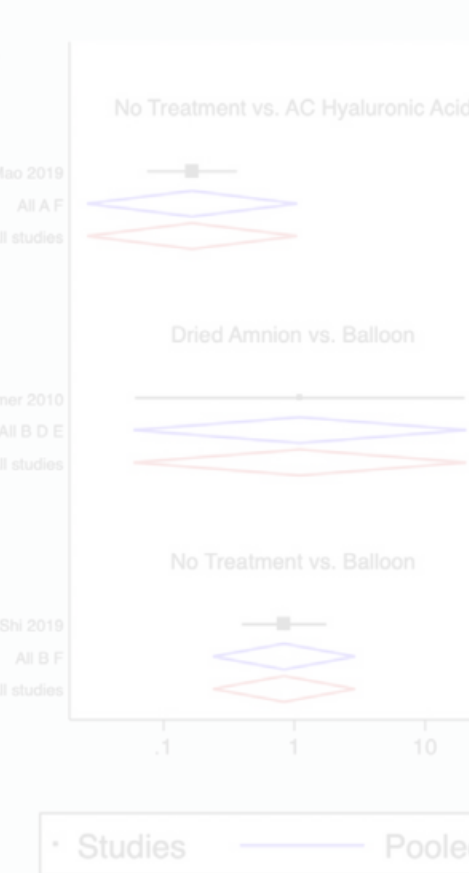


C



# 6. Live birth rate

A



D



Test of consistency:  $\chi^2(1)=0.08, P=0.776$

2-5.

**Comments**



# Principal findings:

**In women diagnosed with IUA who are treated with hysteroscopic lysis of adhesions, mechanical barriers reduced**

- **recurrence of IUA**
- **severity of IUA reformation**
- **improve menstrual patterns**
- **enhance fertility**



# Comparison with existing literature:

- IUA often occurs following **blind curettage for retained products of conception (RPOC)**
- **Hysteroscopic removal** decrease the risk of **IUA formation**
- **Hysteroscopy** is an effective technique for IUA

# **HAG:**

- **water-soluble polymer**
- **safety for human**
- **separate the uterine walls after surgery**
  
- **first-generation HAG: 1 studies**
- **new cross-linked polymer: 4 studies**

# Cook balloon/Foley

(±amnion graft) :

- inflate with a normal saline
- remove after 3 to 5 days /1 week

# Cooper IUD:

- retrieved at the 2<sup>nd</sup> hysteroscopy
- 2–3 months after the initial procedure



# Best Choices

- 1. IUA recurrence: IUD + balloon**
- 2. IUA severity: IUD + HAG**
- 3. Menstrual patterns: balloon  
(±frozen amnion graft)**
- 4. Clinical pregnancy rate: HAG**

# **Strengths**

- **the quality of the selected studies**
- **overall low risk of bias**

# **Limitations**

- **similar SUCRA scores**
- **a paucity of studies for fertility**
- **follow-up 6m vs 6-8w**
- **multiple trials from single centers**

**Thank You**

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