Ectopic Pregnancy: What's Changed and Why It Matters

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No disclosures

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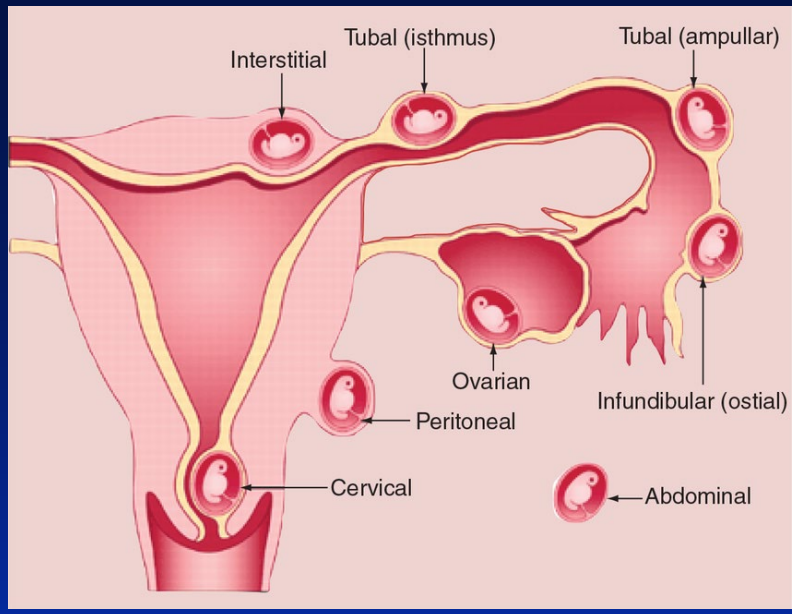
Ectopic Pregnancy Today

- EP is still 1-2% of all pregnancies
- Mortality has dramatically declined: 0.5/100,000
  - Still 6% of pregnancies related deaths/ most common in first trimester
  - Fewer catastrophic ruptures
  - Most now diagnosed with US and hCG algorithms
- Modern management has resulted in new problems and "iatrogenic" error

Modern Management

- Ultrasound needs clinical context (what is a PUL)
- Premature hCG surveillance can result in error
- The Discriminatory Zone is too low
- When you use MTX: Use the 2 dose protocol
- Pregnancy of unknown location (PUL)
  - Active management reduces unscheduled surgery
  - Uterine evacuation reduces time to resolution
  - Women prefer expectant management

Pathophysiology



- Almost a unique human disease

- Tubal transport dysfunction (cilia injury, muscular dysmotility) Smoking, current IUD use
- Altered embryo/tubal signaling ART
- Changes in tubal epithelium (infection, inflammation) PID, Prior EP, Tubal pathology
- More than 50% of EP in women with no risk factor

EDITORIAL

NEJM Evidence

Progestin IUDs and Ectopic Pregnancy — A Call for Context, Not Concern

Authors: Marissa S. Weiss, M.D., M.S.C.E., and Kurt T. Barnhart, M.D., M.S.C.E. Author Info & Affiliations

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VOL. 4 NO. 12 |

Roland N, Kolla E, Poncet L, et al. Intrauterine devices and risk of ectopic pregnancy. *NEJM Evid* 2025;4(12).

EP incidence per 100 person years with LNG IUD:

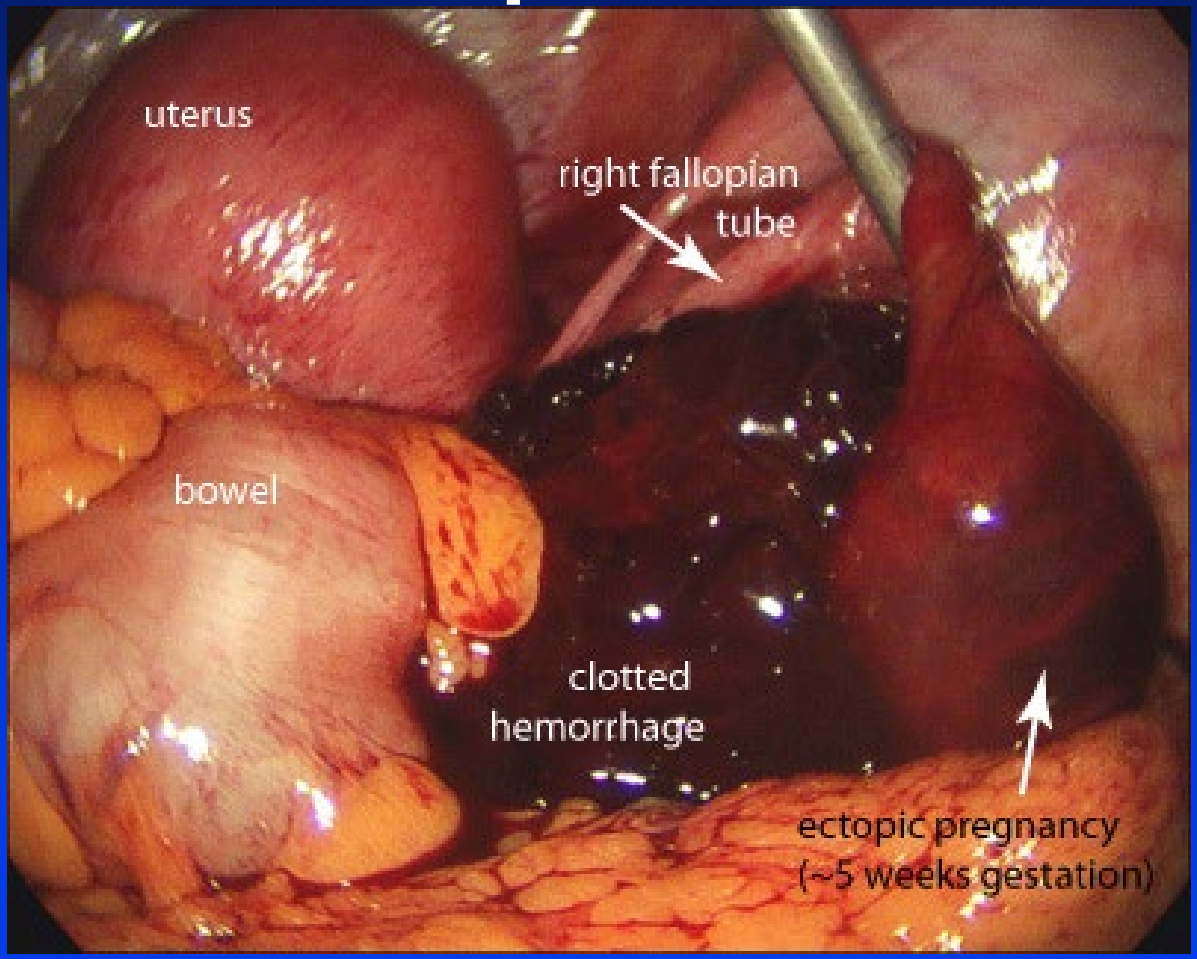
0.18 (13.5 mg), 0.10 (19.5 mg) 0.04 (52 mg), 0.07 (copper)

6.8% 4.1% 1.7% 2.0%

low-dose LNG may selectively impair tubal transport of embryos without fully preventing fertilization

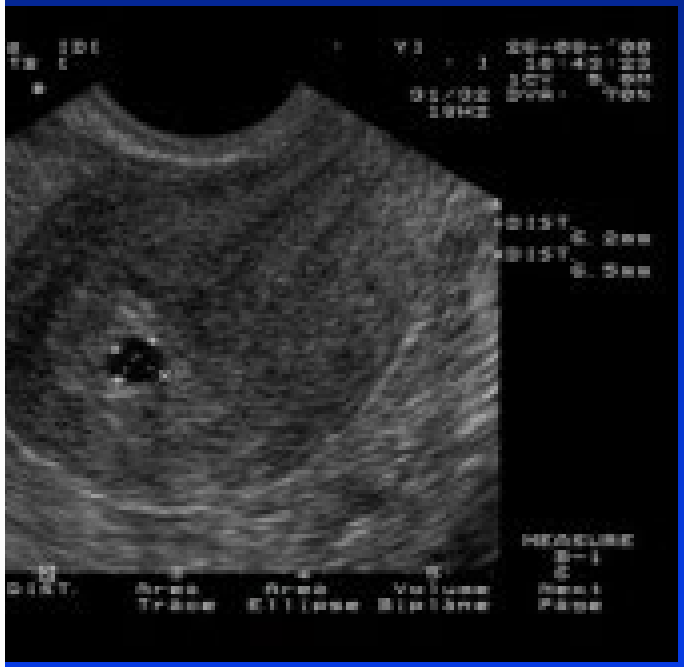
BUT NNT: 743 women to prevent 1 EP with higher dose choice should be by patient consideration not EP risk

Too late:
Ruptured EP



Too Early

Making a definitive dx based on non definitive information



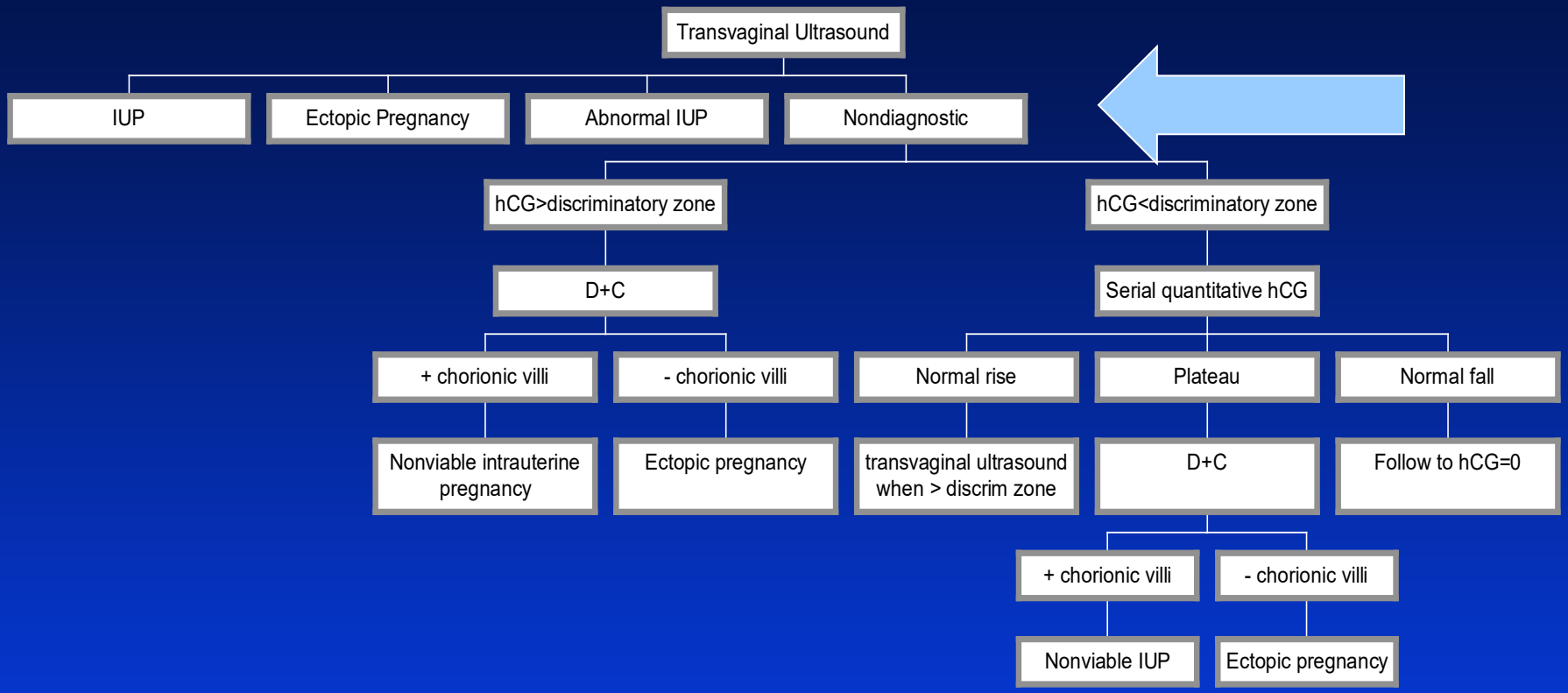


Figure 1. Algorithm for the diagnosis of ectopic pregnancy in a hemodynamically stable patient

Barnhart et al Obstet Gynecol 1994; 84:1010-5
Gracia C, Barnhart KT. Obstet Gynecol, 97(3):464-470, 2001.

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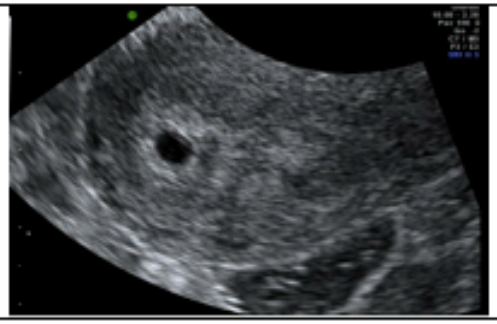
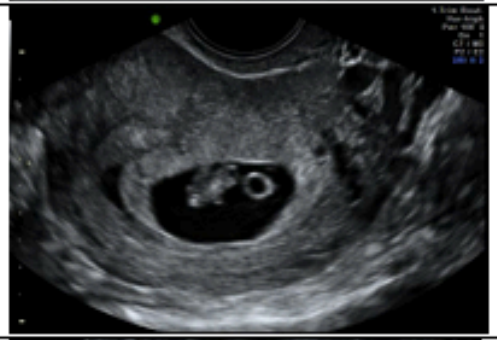
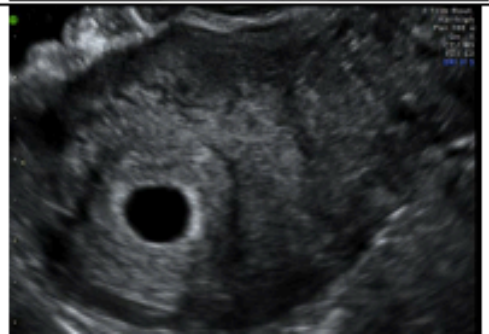
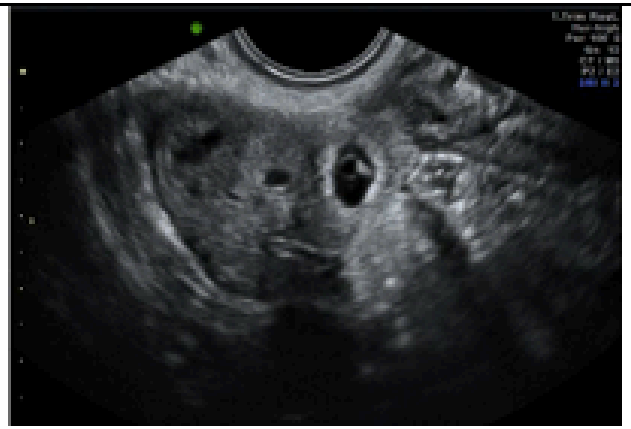
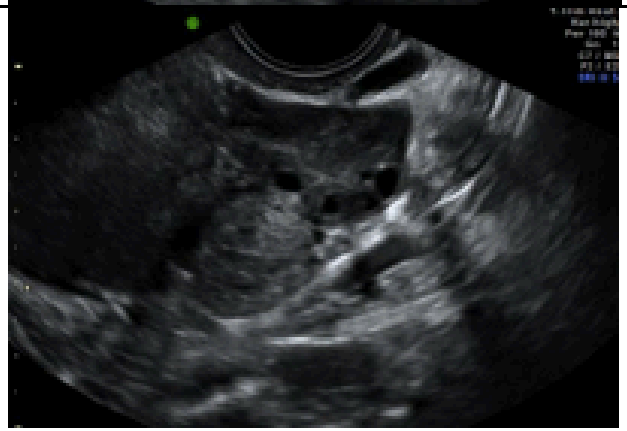
Features visualised on TVS to suggest an IUP		Narrow	Broad
Gestational sac only		Yes	No
Gestation sac with yolk sac		Yes	Yes
Gestation sac with CRL		Yes	Yes
Empty gestation sac (anembryonic)		Yes	No

A saclike structure in the uterus is more likely to be a IUP than Puedosac

The prescience of a YS is Definitive for an IUP

Empty sac > 16 is likely a Miscarriage but may need conformation

Features visualised on TVS to diagnose EP		narrow	broad
Gestation sac with a YS/embryo		Yes	Yes
Empty gestation sac		Yes	No
Inhomogeneous mass		Yes	No
No chorionic villi on uterine curettage and rising hCG level		Persisting PUL	Yes

YS is definitive of EP

"Bagel" sign an be misdiagnosed

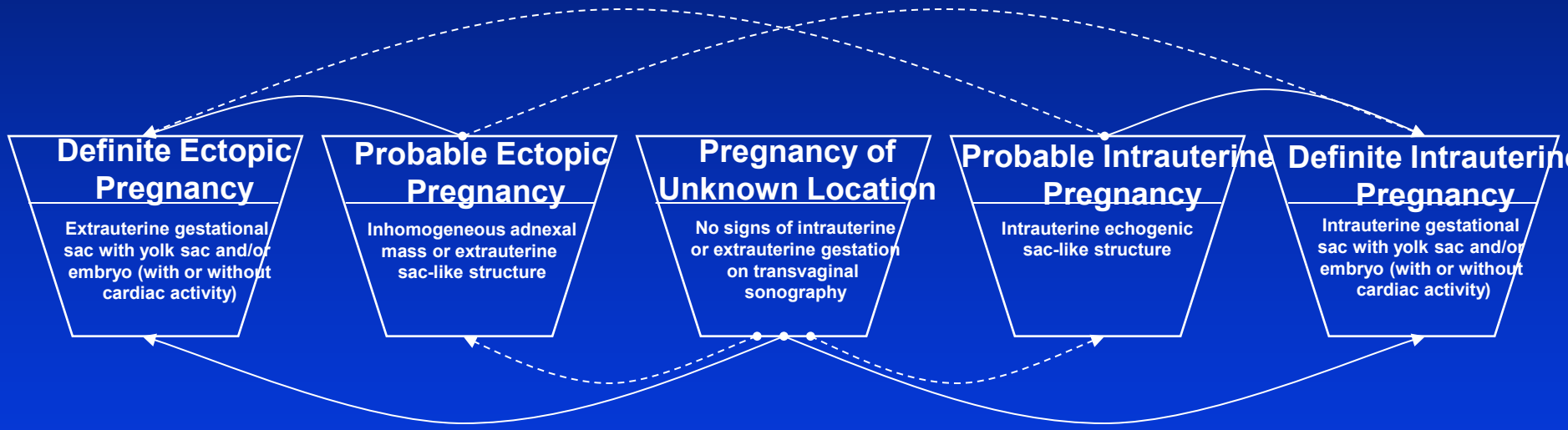
"Blob" sign is suspicious but not definitive

Accuracy of Ultrasound

- TVUS is very accurate when hCG is high
  - Sensitivity 80 - 98%, PPV 90 – 96%
- TVUS not accurate when hCG is low
  - Sensitivity 25 – 33%, PPV 60 – 80%
- Definition of EP matters
  - EP “definitive” Sens 13%, PPV 98%
  - EP “suspicious” Sens 42%, PPV 80%

Barnhart KT. Obstet Gynecol 1999; 94(4):583-587
Barnhart KT, Obstet Gynecol 2010; 117: 299-306.

Classification scheme for women with a positive pregnancy test at first transvaginal sonography (TVS)



What is the Discriminatory Zone?

- The best DZ is gestational age
  - 5 5/7 weeks (40 days) regardless of number of gestations
- Not all women know their LMP
  - Maybe off by days, or at times off by 4 weeks
- DZ is a Surrogate for gestation age
  - Level at which normal milestones should be identified (gestational sac): the level does not discriminate location

Discriminatory Zone

- What has changed?
  - IRP has changed so now 1500 first IU is about 1900 4rth IU
  - Most women get US in first trimester (even without symptoms)
  - Ruptured EP uncommon, clinician very aware of risk
    - More scans = more false positives (false negatives)
    - Effort has shifted to avoid interruption of a desired IUP
    - Methotrexate is common and easy to administer

Diagnostic Criteria for Nonviable Pregnancy Early in the First Trimester

Table 3. Diagnostic and Management Guidelines Related to the Possibility of a Viable Intrauterine Pregnancy in a Woman with a Pregnancy of Unknown Location.*

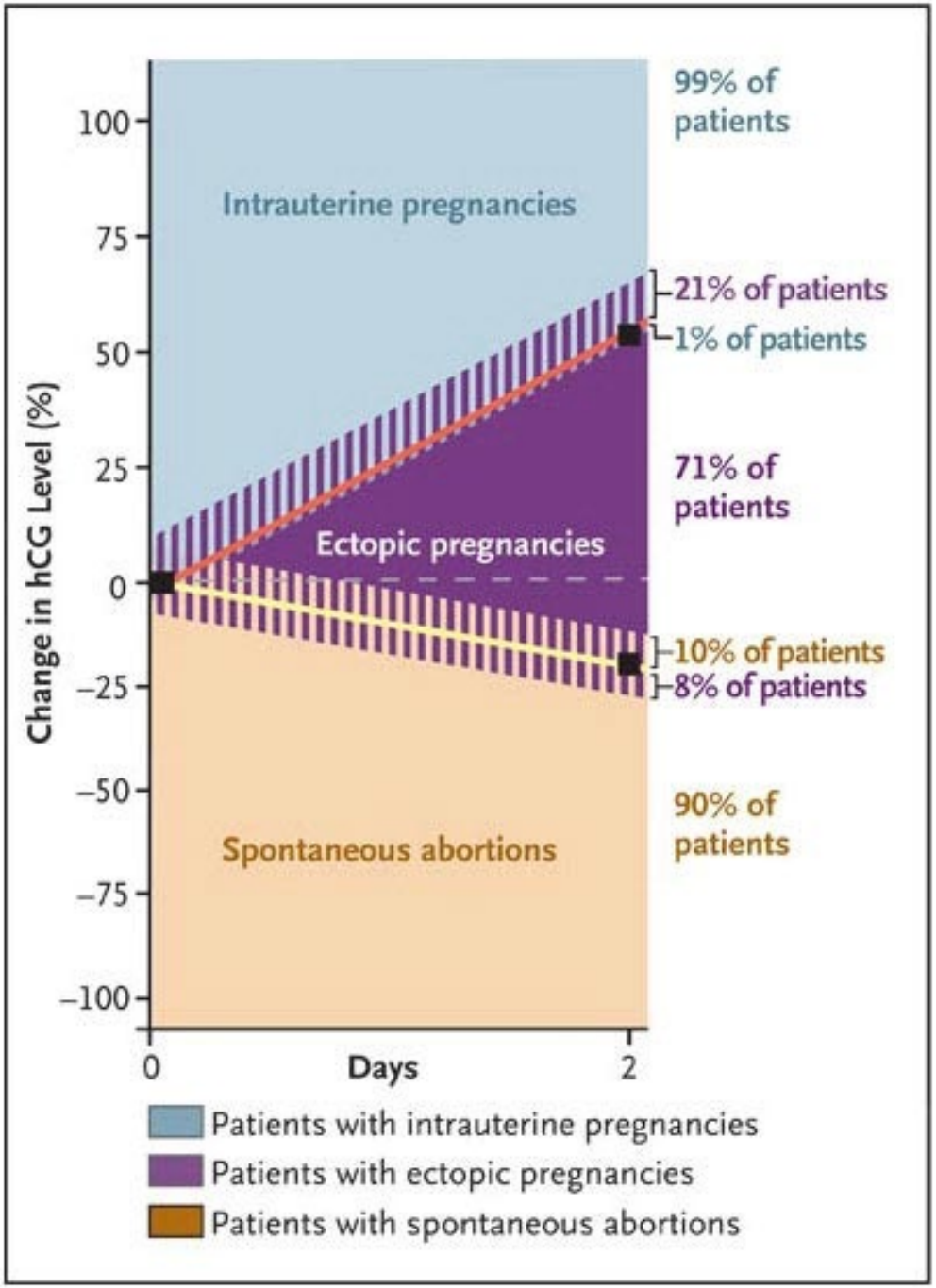
Finding	Key Points
No intrauterine fluid collection and normal (or near-normal) adnexa on ultrasonography†	A single measurement of hCG, regardless of its value, does not reliably distinguish between ectopic and intrauterine pregnancy (viable or nonviable). If a single hCG measurement is <3000 mIU/ml, presumptive treatment for ectopic pregnancy with the use of methotrexate or other pharmacologic or surgical means should not be undertaken, in order to avoid the risk of interrupting a viable intrauterine pregnancy. If a single hCG measurement is ≥3000 mIU/ml, a viable intrauterine pregnancy is possible but unlikely. However, the most likely diagnosis is a nonviable intrauterine pregnancy, so it is generally appropriate to obtain at least one follow-up hCG measurement and follow-up ultrasonogram before undertaking treatment for ectopic pregnancy.
Ultrasonography not yet performed	The hCG levels in women with ectopic pregnancies are highly variable, often <1000 mIU/ml, and the hCG level does not predict the likelihood of ectopic pregnancy rupture. Thus, when the clinical findings are suspicious for ectopic pregnancy, transvaginal ultrasonography is indicated even when the hCG level is low.

Ectopic Pregnancy

Kurt T. Barnhart, M.D., M.S.C.E

N Engl J Med 2009; 361:379-387

. Change in the hCG Level in Intrauterine Pregnancy, Ectopic Pregnancy, and Spontaneous Abortion.



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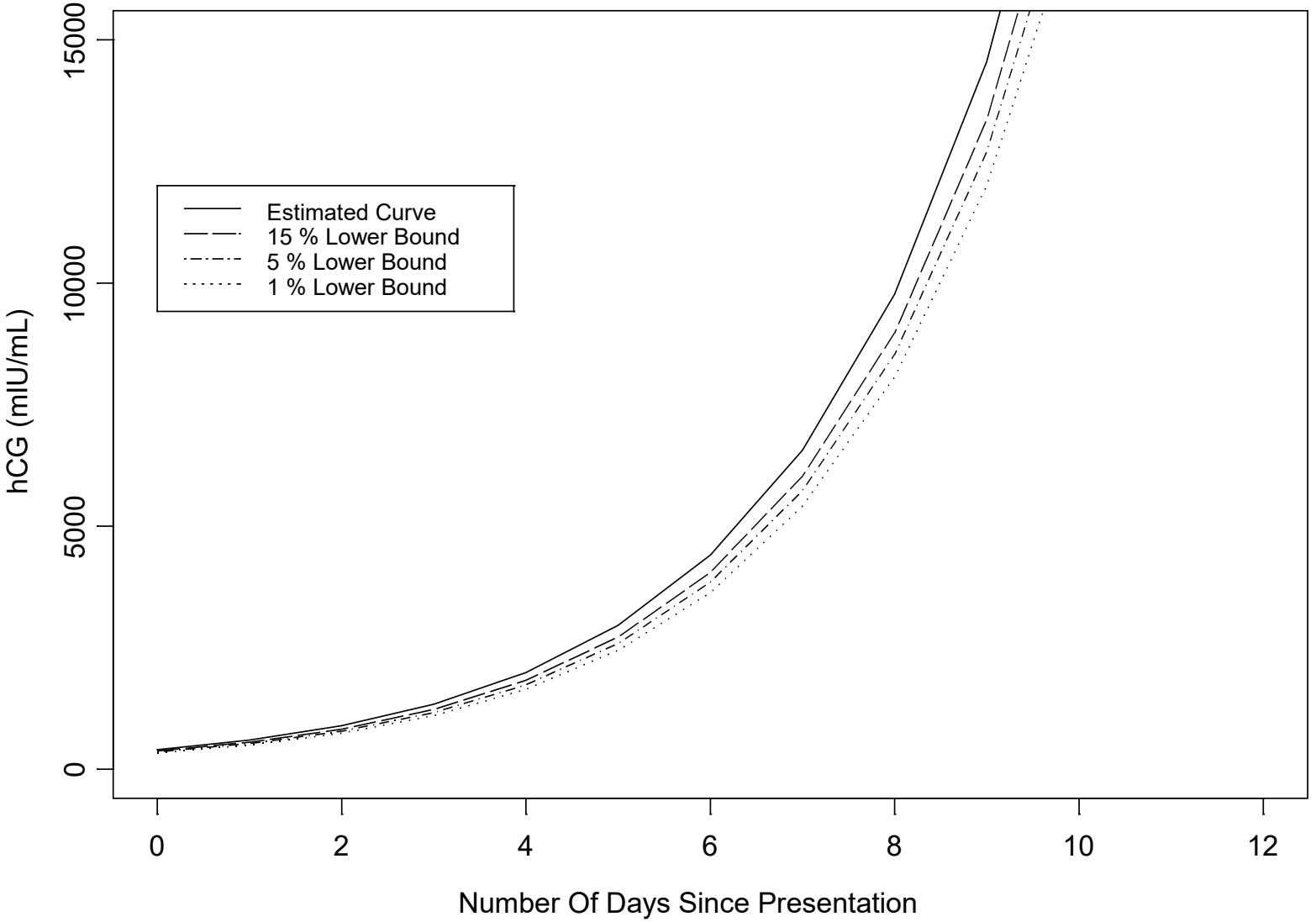
Increase in hCG value at different days (as a percent of initial value)

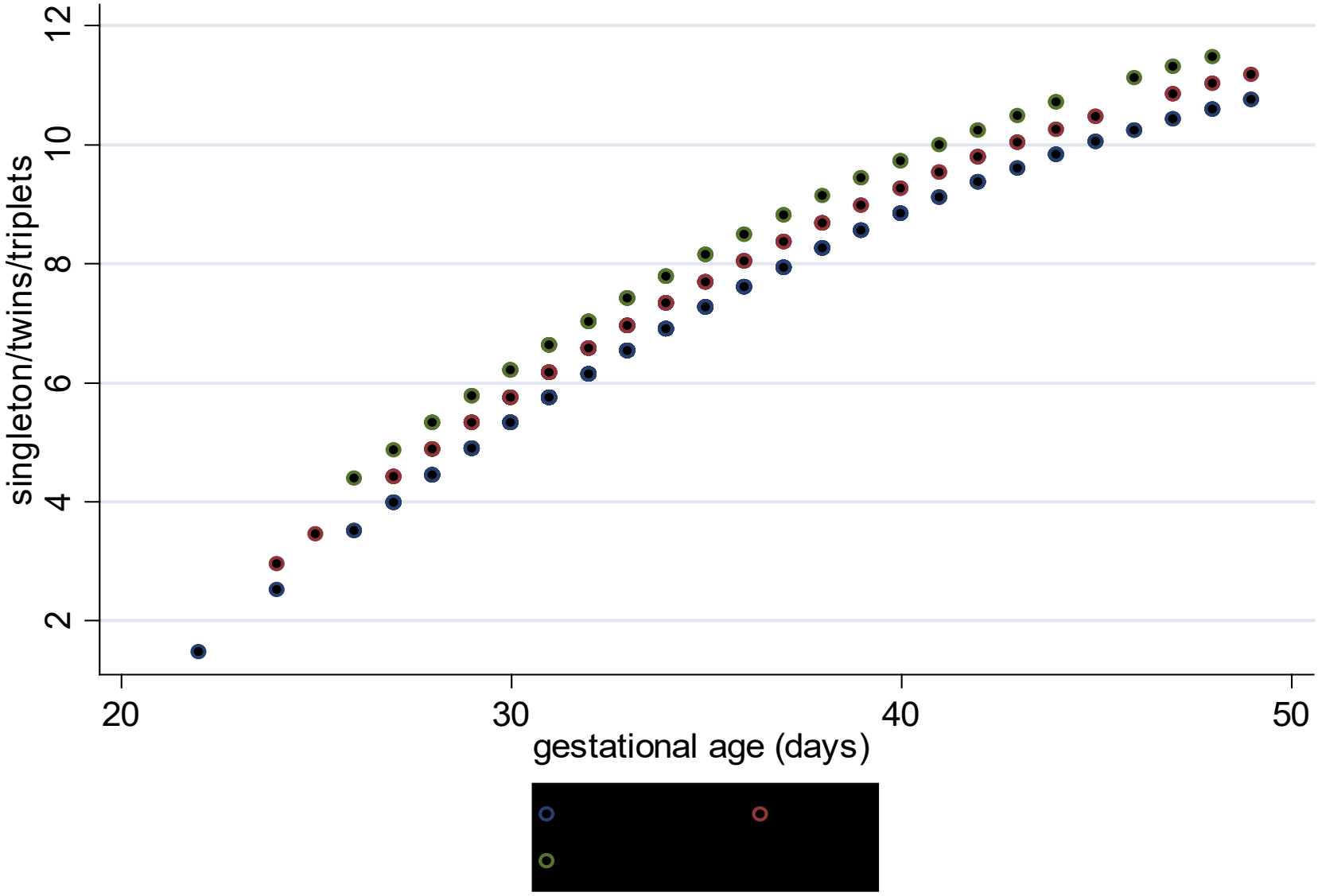
quartile	slope	1 day	2 day	3 days	4 days
99	1.23	1.23	1.53	1.84	2.26
95	1.30	1.30	1.69	2.19	2.84
85	1.37	1.36	1.87	2.55	3.48
50	1.50	1.50	2.22	3.31	4.94
10	1.66	1.66	2.76	4.58	7.60
1	1.81	1.81	3.29	5.96	10.80

Barnhart KT. Symptomatic Patients with an Early Viable Intrauterine Pregnancy; hCG Curves Redefined. Obstet Gynecol 2004;104:50-5.



Barnhart KT. Symptomatic Patients with an Early Viable Intrauterine Pregnancy: hCG Curves Redefined. Obstet Gynecol 2004;104:50-5

hCG Rise After IVF

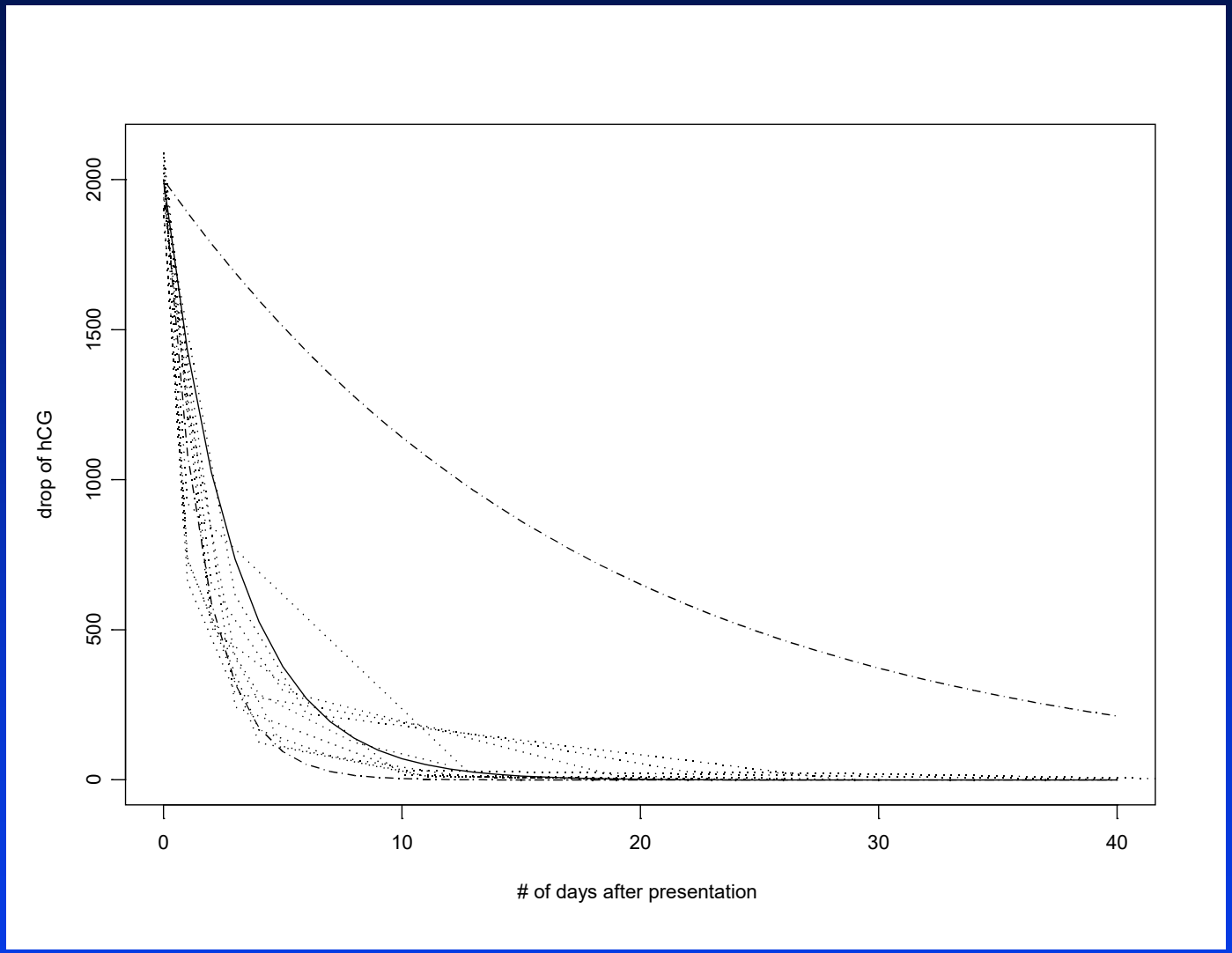


Rise in hCG Depends on Value

- **The hCG rise in IUP differs by patient factors, and level at presentation.**
- **The 2-day (1st percentile) rise: faster when hCG values are low slower when hCG values are high.**

Initial hCG	<1500	1500-3000	> 3000
1% rise	49%	40%	33%

Curve of Complete Spontaneous Abortion (SAB)



Barnhart, K. Decline of serum human chorionic gonadotropin and spontaneous complete abortion: Defining the normal curve. Ob Gyn 2004:104(5):975-981.

Methotrexate

- You have made a definitive diagnosis of ectopic pregnancy. What methotrexate protocol do you use?
  - Single dose
  - Multiple dose
  - Two dose

Odds ratio of failure of “single dose" vs. “multiple dose"

	OR	95% CI	p
Analysis of all data	1.71	1.04 - 2.82	0.03
Analysis controlled for actual hCG value**	2.34	1.05 - 5.23	0.04
Analysis controlled for estimated hCG value and EHA	4.74	1.77 – 12.62	0.02

“Single-dose” is more commonly used:

- Ease of use
- Fewer visits
- Fewer injections

CI = confidence interval; EHA = Embryonic heart activity

Two-Dose Management of EP

- Single dose 50 mg/m^2 MTX (nomogram)
  - Baseline, day 4, day 7
- Multiple dose 1 mg/kg MTX, 0.1 mg/kg Leucovorin
  - "Daily" until 15% decline from previous day
- **TWO DOSE 50 mg/m^2**
  - **Same number of visits as "single dose"**
  - **BUT GIVE SECOND DOSE ON DAY 4**
  - **Repeat dose(s) based on hCG on day 4 – 7 (or 7-11)**

Meta-Analysis > Int J Gynaecol Obstet. 2018 Jun;141(3):295-303. doi: 10.1002/ijgo.12473. Epub 2018 Mar 15.

Systematic review and meta-analysis of single-dose and non-single-dose methotrexate protocols in the treatment of ectopic pregnancy

Jin-Sung Yuk [1], Jung Hun Lee [1], Won I Park [2], Hyeong Sik Ahn [3], Hyun Jung Kim [3]

Affiliations + expand

PM

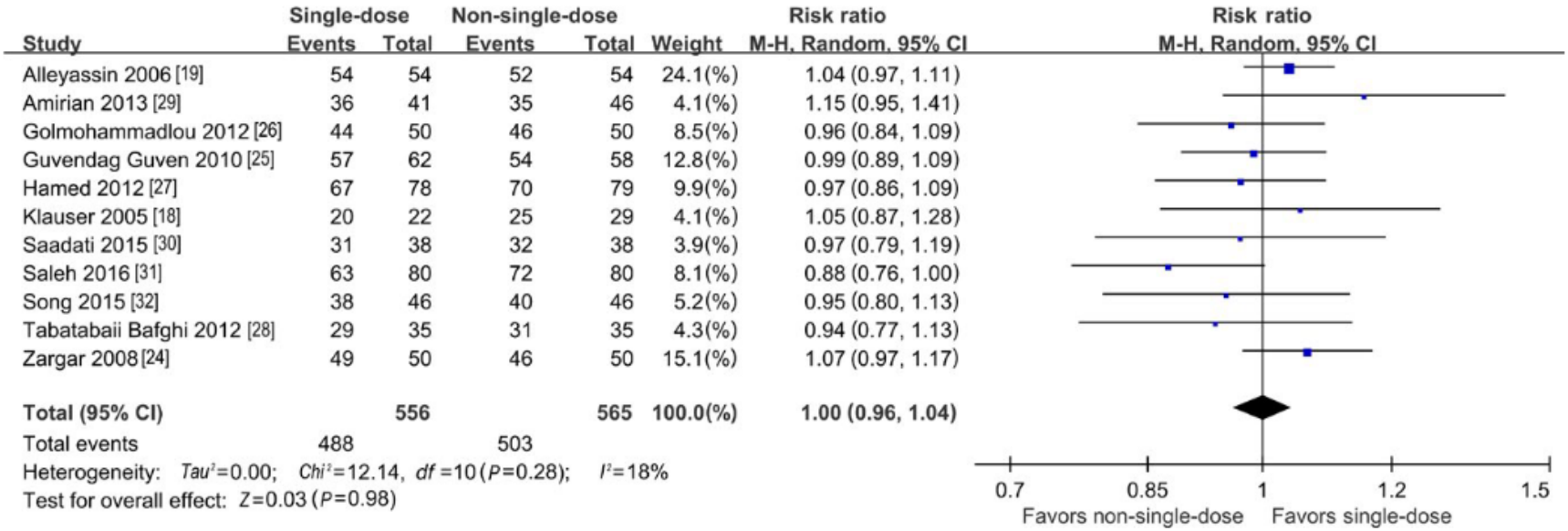


FIGURE 2 Success rate in the treatment of ectopic pregnancy. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel test; Random, random-effects model.

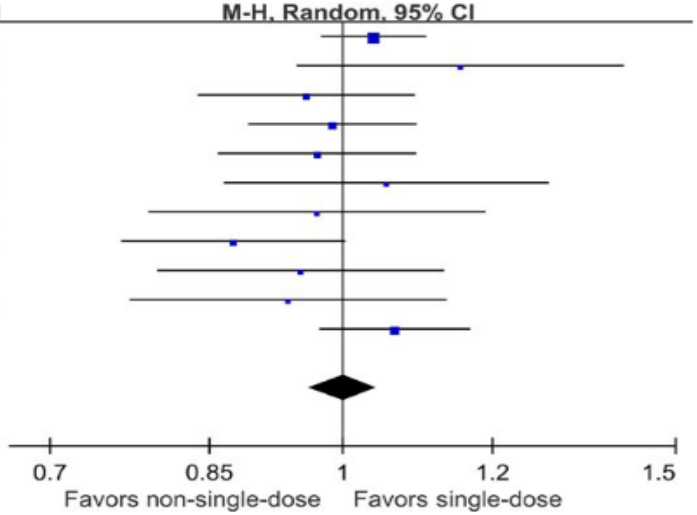
Main results: The single-dose and non-single-dose protocols had similar success rates (RR 1.00, 95% CI 0.96-1.04; 11 trials, 1121 patients, I^2 =18%). The non-single-dose protocols had a higher adverse effect rate than did the single-dose protocol (RR 0.73, 95% CI 0.59-0.91; nine trials, 934 patients, I^2 =0%).

Conclusions: The single-dose methotrexate protocol was the optimal protocol for the medical treatment of ectopic pregnancy.

Study	Single-dose Events	Total	Non-single-dose Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Alleyassin 2006 [19]	54	54	52	54	24.1(%)	1.04 (0.97, 1.11)
Amirian 2013 [29]	36	41	35	46	4.1(%)	1.15 (0.95, 1.41)
Golmohammadlou 2012 [26]	44	50	46	50	8.5(%)	0.96 (0.84, 1.09)
Guvendag Guven 2010 [25]	57	62	54	58	12.8(%)	0.99 (0.89, 1.09)
Hamed 2012 [27]	67	78	70	79	9.9(%)	0.97 (0.86, 1.09)
Klauser 2005 [18]	20	22	25	29	4.1(%)	1.05 (0.87, 1.28)
Saadati 2015 [30]	31	38	32	38	3.9(%)	0.97 (0.79, 1.19)
Saleh 2016 [31]	63	80	72	80	8.1(%)	0.88 (0.76, 1.00)
Song 2015 [32]	38	46	40	46	5.2(%)	0.95 (0.80, 1.13)
Tabatabaii Bafghi 2012 [28]	29	35	31	35	4.3(%)	0.94 (0.77, 1.13)
Zargar 2008 [24]	49	50	46	50	15.1(%)	1.07 (0.97, 1.17)
Total (95% CI)		**556**		**565**	**100.0(%)**	**1.00 (0.96, 1.04)**
Total events	488		503			

Heterogeneity: $Tau^2=0.00$; $Chi^2=12.14$, $df=10$ ($P=0.28$); $I^2=18\%$

Test for overall effect: $Z=0.03$ ($P=0.98$)



Alleyassin : the N, success rate, and the RR of the paper are not correct in the meta-analysis

Amiria: this is a resident's thesis in Iran; it is not properly blinded and likely not randomized.

Golmohamadlou: Only the abstract of the paper is in English, there is no blinding.

Hamed: Incorrect numbers and RR are in the meta-analysis, and do not reflect the raw data

Klauser: This is an unpublished abstract at a meeting and is not a manuscript

Saadati: The number from the papers are not the same used in the meta-analysis

Song: this is a well-done study with the effect opposite of what the author of the meta-analysis claim is the summary finding. Of note this paper Falsely has one of the lowest weights

Zargar: not at randomized trial. Conducted in Iran with enrollment "one by one" with inclusion criteria vastly different form the use of MTX in other studies.

This paper at best is very, very sloppy. *However, given that all "errors" are in one directly, I think this is fraud.*

Of note, I reviewed this paper for two journals (rejected). This paper was simply readdressed and published unchanged.

Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis

Snigdha Alur-Gupta, MD; Laura G. Cooney, MD; Suneeta Senapati, MD, MSCE; Mary D. Sammel, ScD; Kurt T. Barnhart, MD, MSCE

AJOG at a Glance

Why was this study conducted?

This study was conducted to compare the odds of treatment success, side effects, surgery for ruptured ectopic pregnancy, and length of follow-up of commonly used methotrexate protocols for the treatment of ectopic pregnancy.

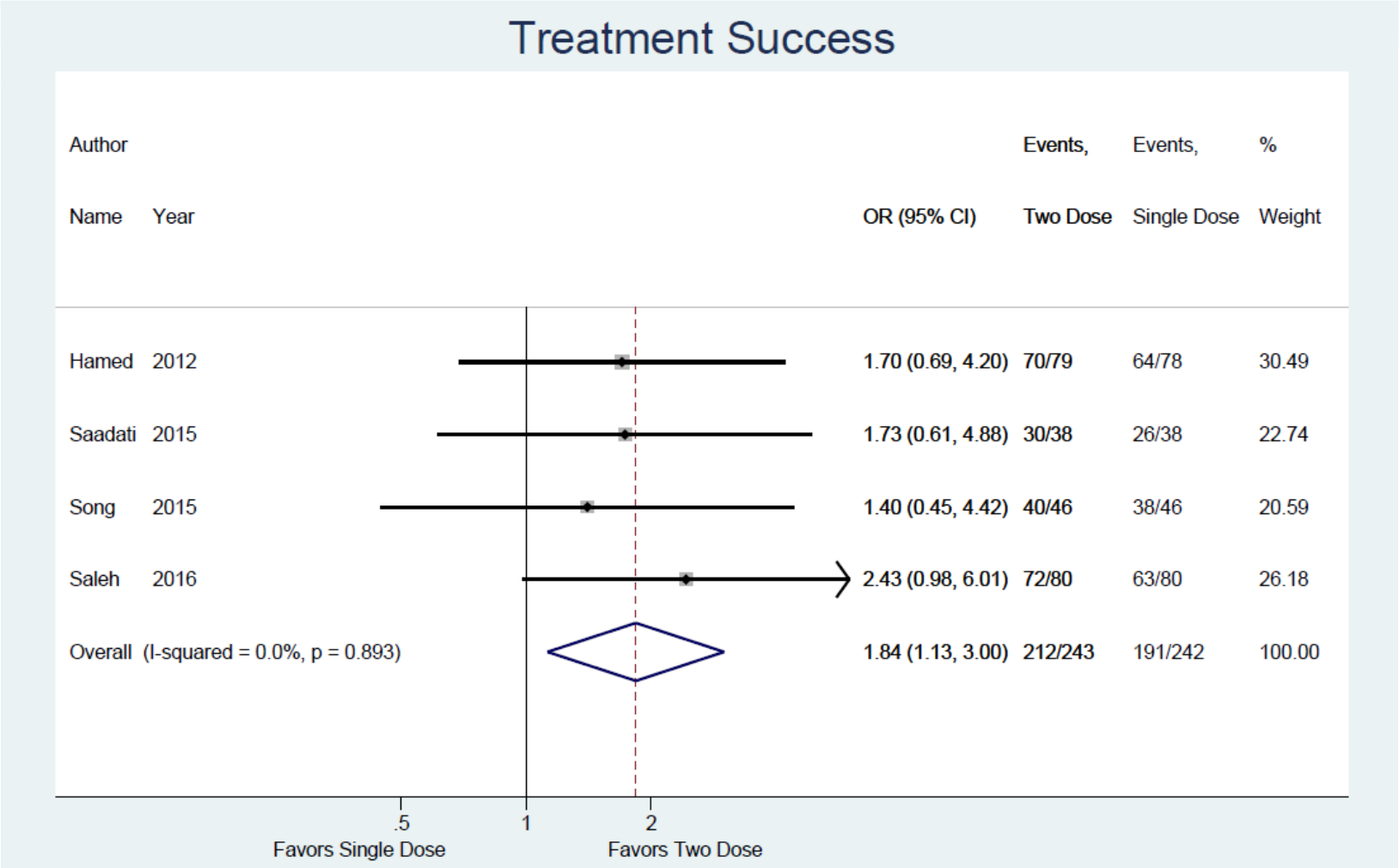
Key findings

The 2-dose protocol was superior to the single-dose protocol in treatment success, including in women at higher risk for failure, such as those with high human chorionic gonadatropin and large adnexal mass.

What does this add to what is known?

This adds an updated meta-analysis of a 2-dose versus a single-dose protocol and additional analyses of a multi-dose versus a single-dose protocol using only quality randomized controlled trials.

Two dose vs Single dose: Meta-Analysis



Two Dose Methotrexate

- Overall almost two time more successful than single dose
  - 1.84 (1.83 – 3.00)
- More successful when there is a mass
  - 2.92 (1.23 – 6.93)
- More successful when there is a high hcg
  - 3.23 (1.53 – 6.89)
- Decreased the time to resolution by 7 days
  - - 7.87 (-12.23 – -3.52)
- TWO DOSE MTX SHOULD BE FIRST LINE TREATMENT

JAMA | Original Investigation

Effect of an Active vs Expectant Management Strategy on Successful Resolution of Pregnancy Among Patients With a Persisting Pregnancy of Unknown Location
The ACT or NOT Randomized Clinical Trial

Kurt T. Barnhart, MD; Karl R. Hansen, MD; Mary D. Stephenson, MD; Rebecca Usadi, MD; Anne Z. Steiner, MD; Marcelle I. Cedars, MD; Emily S. Jungheim, MD; Kathleen M. Hoeger, MD; Stephen A. Krawetz, PhD; Benjie Mills, MD; Meredith Alston, MD; Christos Coutifaris, MD; Suneeta Senapati, MD; Sarita Sonalkar, MD; Michael P. Diamond, MD; Robert A. Wild, MD; Mitchell Rosen, MD; Mary D. Sammel, ScD; Nanette Santoro, MD; Esther Eisenberg, MD; Hao Huang, MD; Heping Zhang, PhD; for the Reproductive Medicine Network

- **Expectant management consisted of monitoring of serial hCG values every 4–7 days.**
- **Uterine evacuation consisted of uterine evacuation followed by methotrexate in those who did not have a decline in hCG of at least 15% one day after the procedure**
- **Empiric treatment with methotrexate consisted of initiation of methotrexate**

Methotrexate in both active treatment arms followed the 2 dose protocol

Alur-Gupta S, Barnhart KT. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. Am J Obstet Gynecol 2019;221(2):95-108.)

Active vs Expectant Management

- **Superiority of active compared to expectant management for women with a persisting pregnancy of unknown location.**
  - A greater number of women successfully resolved the pregnancy uneventfully with active compared to expectant management.
  - There was at least a 50% reduction in the number of unscheduled surgical and medical interventions

- **Successful resolution with active treatment (96%) was higher than in previous trials (range 74-90%).**
  - The two dose methotrexate protocol is superior to single dose methotrexate ectopic pregnancy
  - This trial supports its use in women with a PPUL.

Uterine Evacuation vs Methotrexate

- **First randomized trial to compare uterine evacuation to empiric methotrexate in women with a PPUL.**
  - **These data demonstrate that the two strategies were both very effective and non-inferior.**
  - **The use of uterine evacuation followed by methotrexate only in those without a decline in hCG resulted in a shorter time to resolution of 6 – 8 days.**
  - **Side effects more common with methotrexate.**

- **Shorter time to resolution due to 44 % (27/62) who received uterine evacuation needed no further treatment.**
  - **Methotrexate was administered 24 hours after uterine evacuation only if hCG concentration failed to decline by at least 15%.**

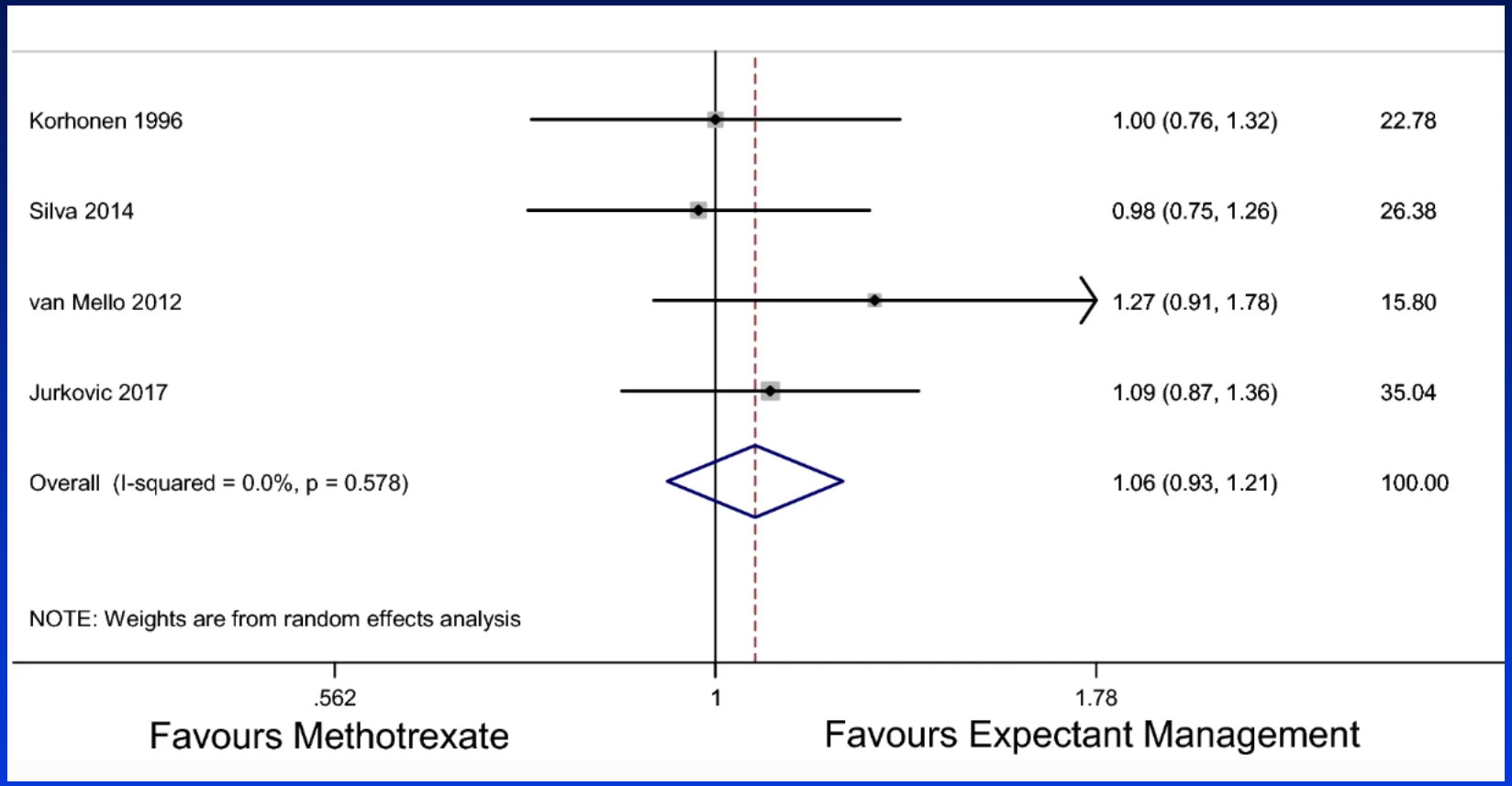
Choice and Shared Decision Making

- **A majority of women found the treatment they received satisfactory and acceptable.**
  - **However, women preferentially crossed over to, and expressed a stronger preference for, expectant management**

- **Six out of ten (59%) women achieved uneventful successful resolution with expectant management.**
  - **This was slightly lower than the 74- 100% found in previous studies**

During this stressful time period, it is possible that women would prefer a chance at resolution without active management and find an increased need for unscheduled intervention an acceptable trade off.

Expectant Management vs MTX



Most hCG < 2000

Archives of Gynecology and Obstetrics (2022) 305:547–553
https://doi.org/10.1007/s00404-021-06236-y

REVIEW

Methotrexate versus expectant management in ectopic pregnancy: a meta-analysis

Ahmed Kunwer Naveed[1] · Muhammad Umair Anjum[1] · Ali Hassan[1] · Sumbal Nasir Mahmood[2]

Modern Management

- Ultrasound needs clinical context
- Premature hCG surveillance can result in error
- The Discriminatory Zone is too low
- When you use MTX: Use the 2 dose protocol
- Pregnancy of unknown location (PUL)
  - Active management reduces unscheduled surgery
  - Uterine evacuation reduces time to resolution
  - Women prefer expectant management