Pregnancies of Unknown Location

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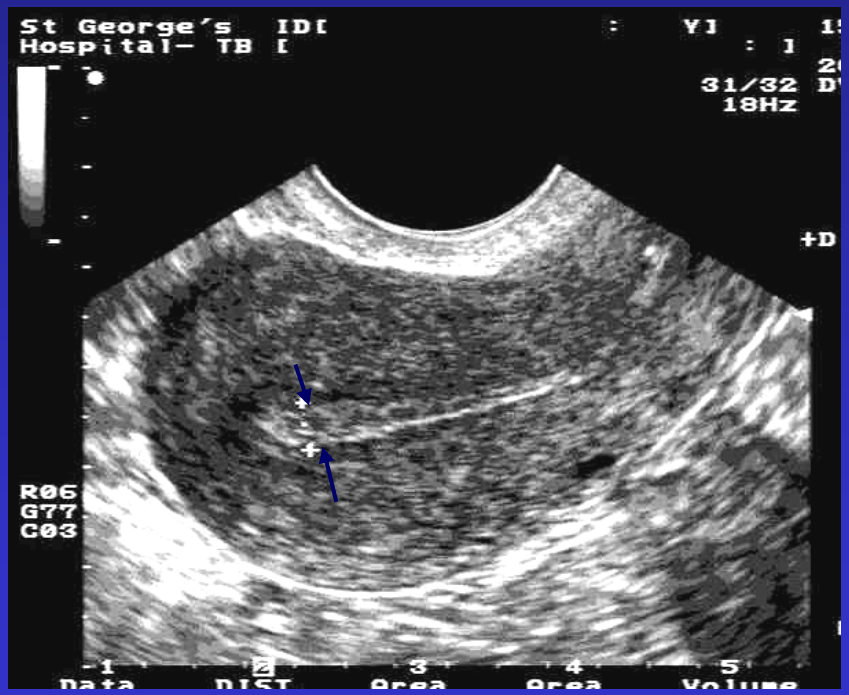
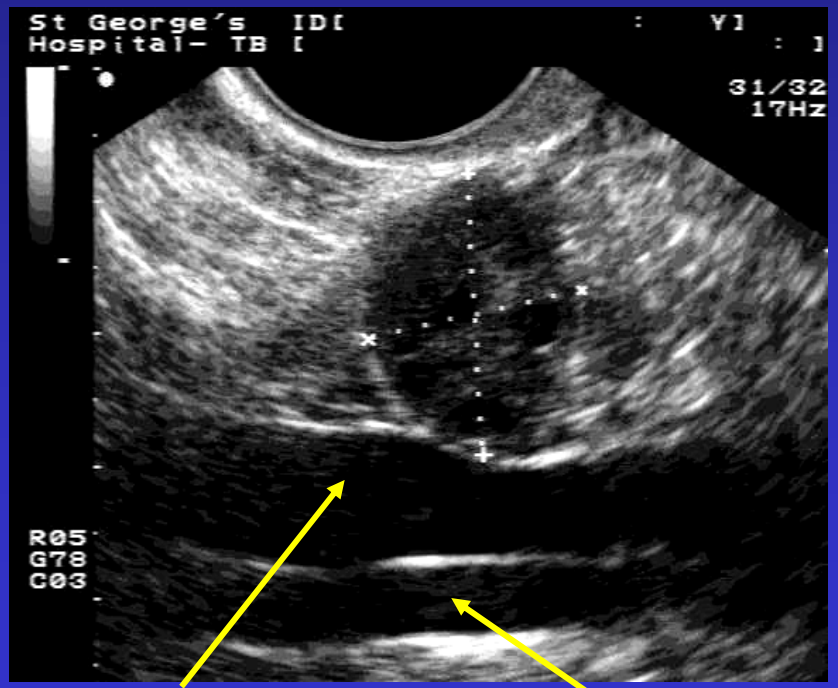
Whittington Hospital, London

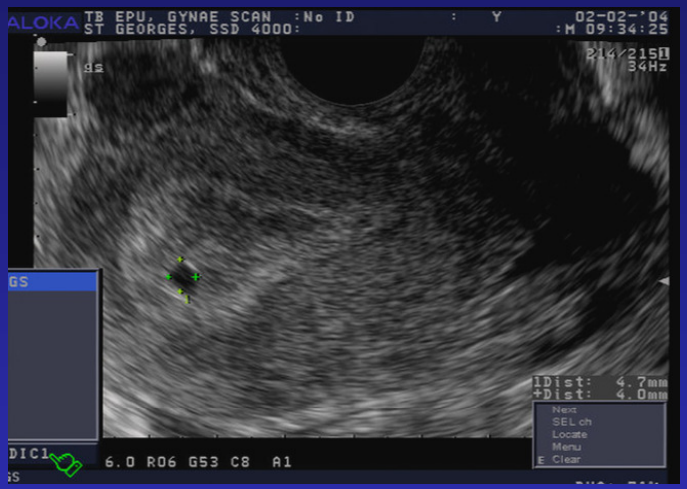
Pregnancy of Unknown Location (PUL)

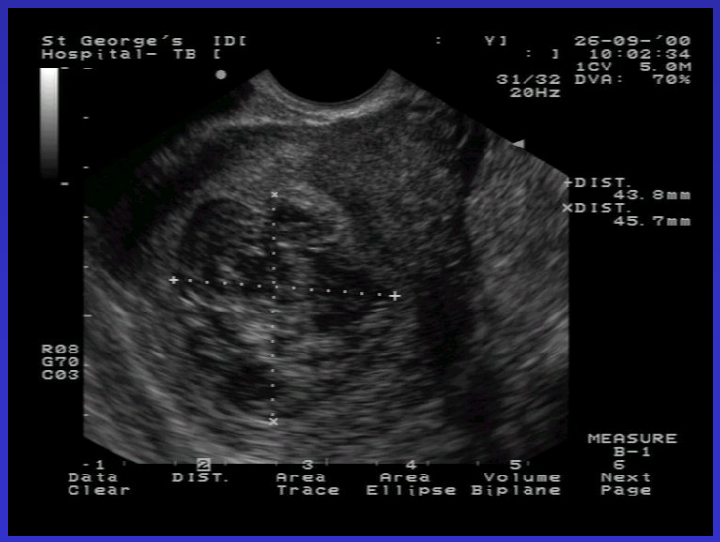
- Positive pregnancy test
- No pregnancy visualised on scan
- Not interchangeable with ‘ectopic pregnancy’

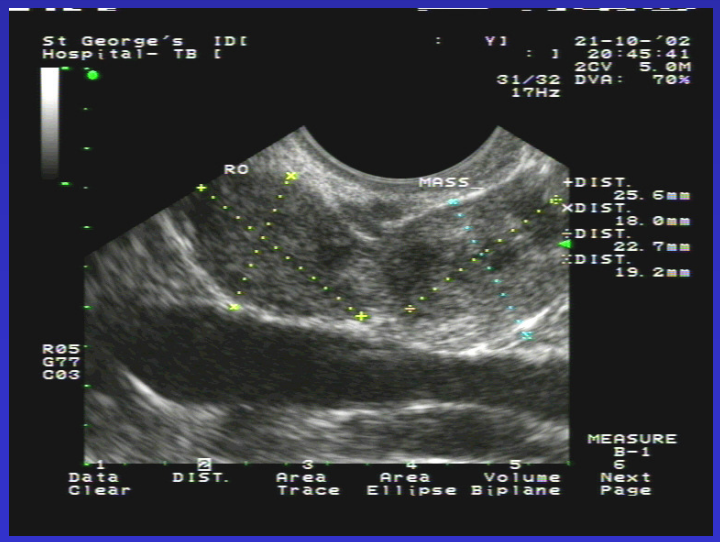




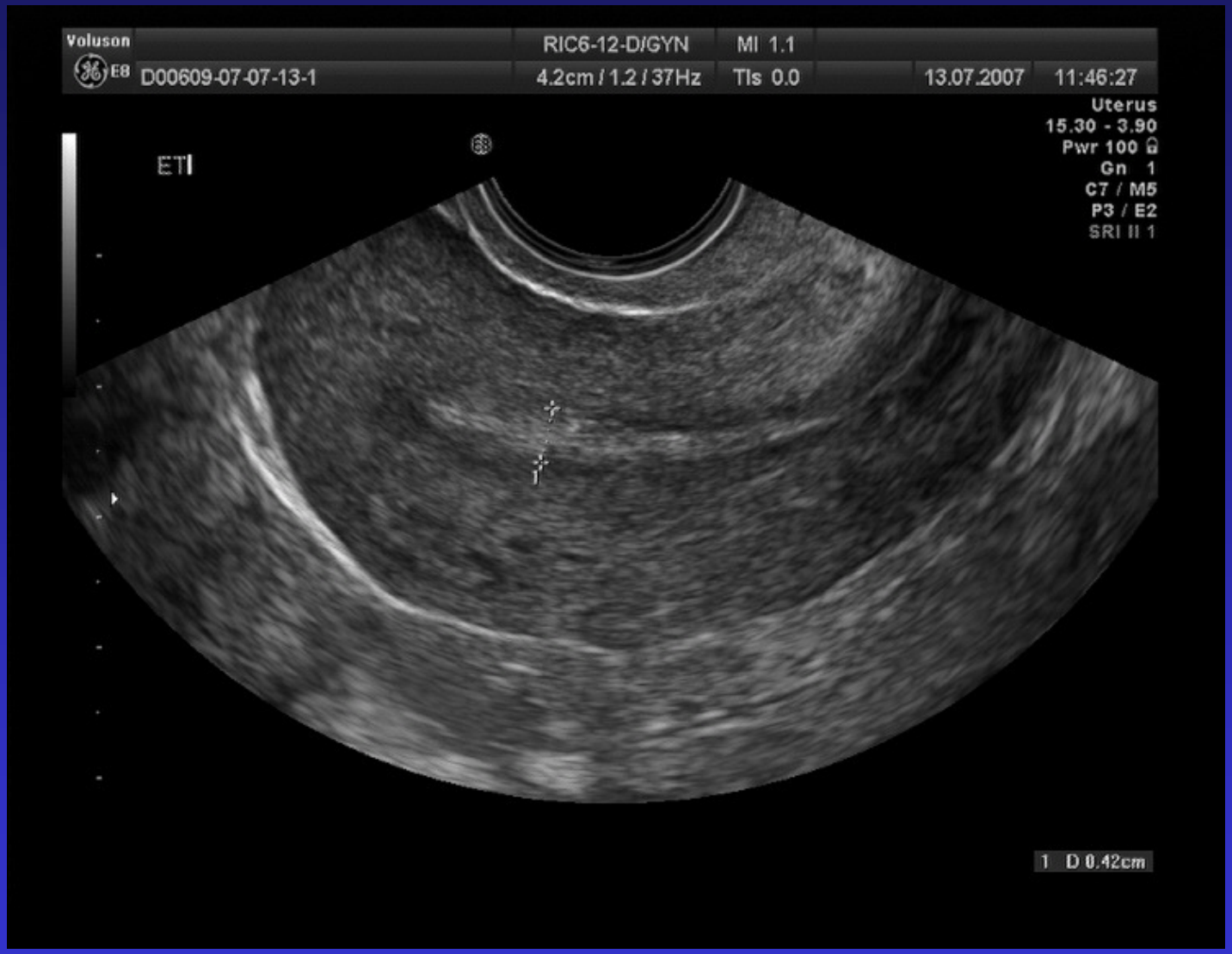
X Pregnancies of Unknown Location



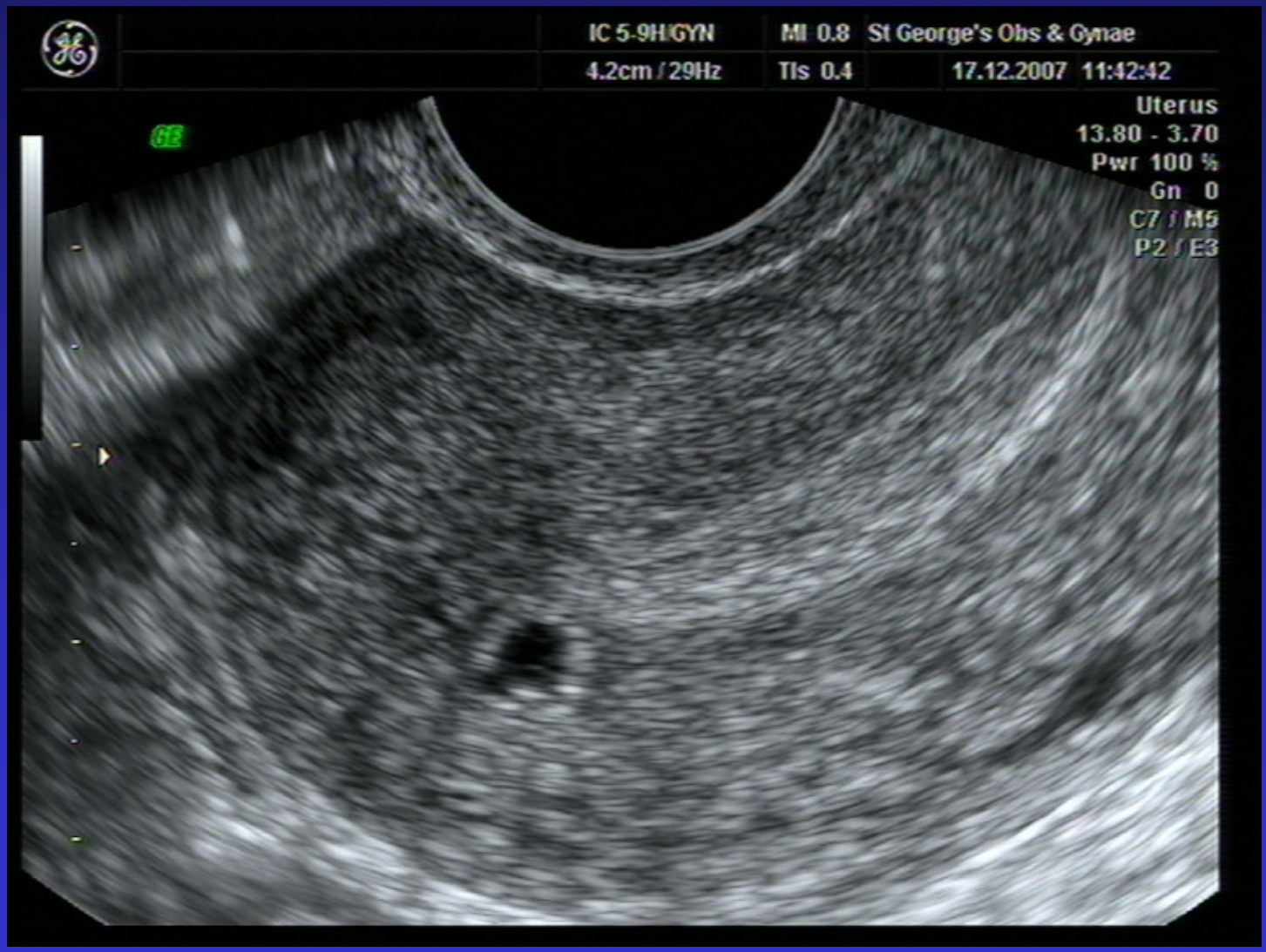




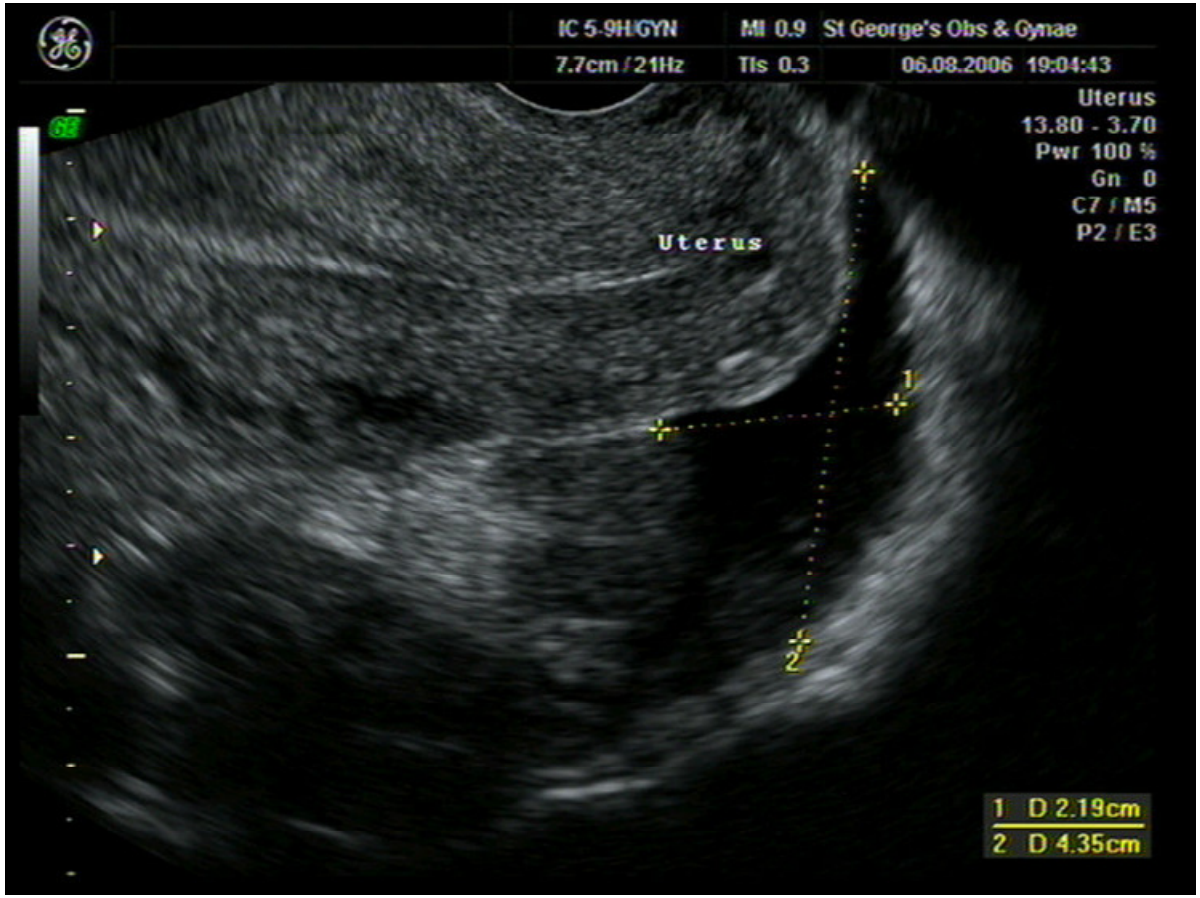
9/40 Heavy bleeding with clots



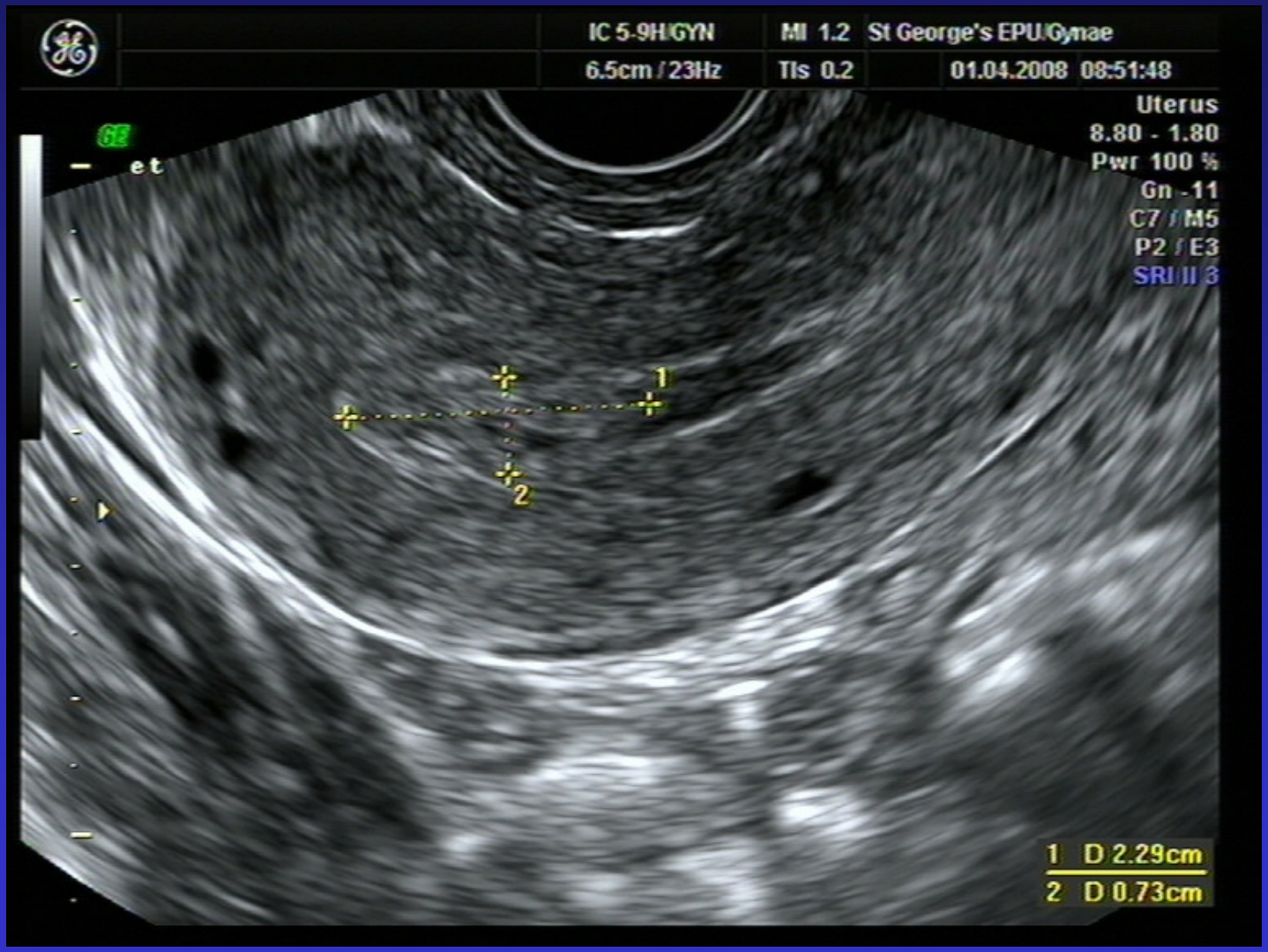
5/40 Light PV bleeding



?/40 Lower abdominal discomfort



7/40 Moderate vaginal bleeding



Positive Pregnancy Test

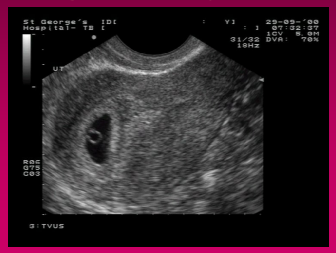
TVS

70-90%

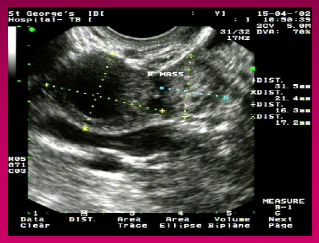
10-30%

Diagnostic

Intra-Uterine Pregnancy (IUP)



Ectopic Pregnancy (EP)



Non-diagnostic

Pregnancy of Unknown Location

- Failing PUL
- IUP
- EP
- Persistent PUL

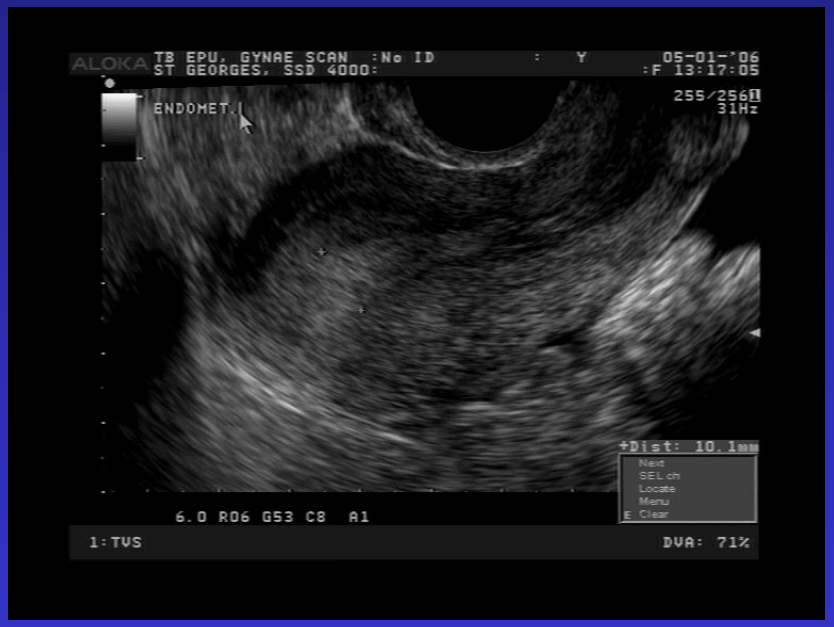
50-70%

7-20%

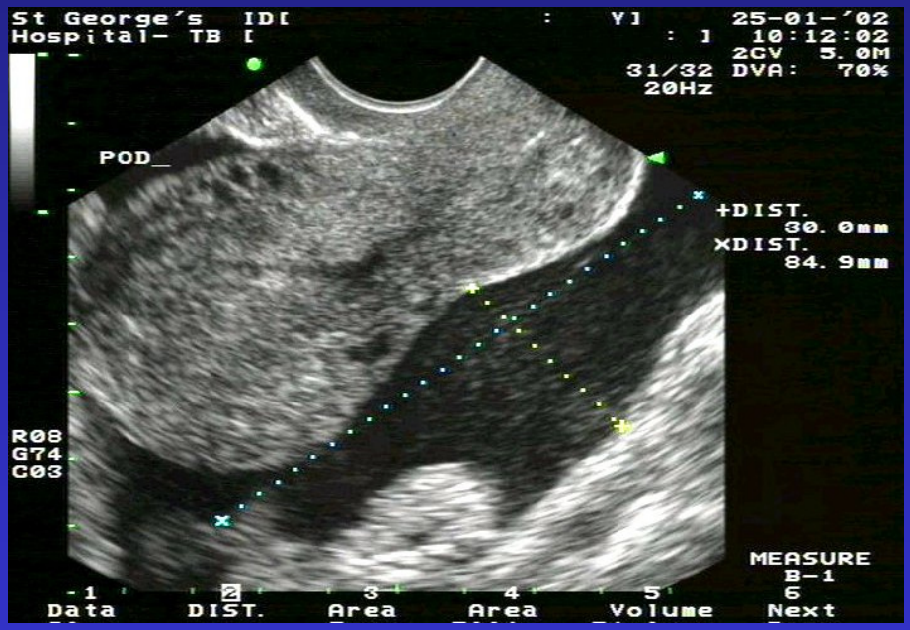
Practical Advice - PULs

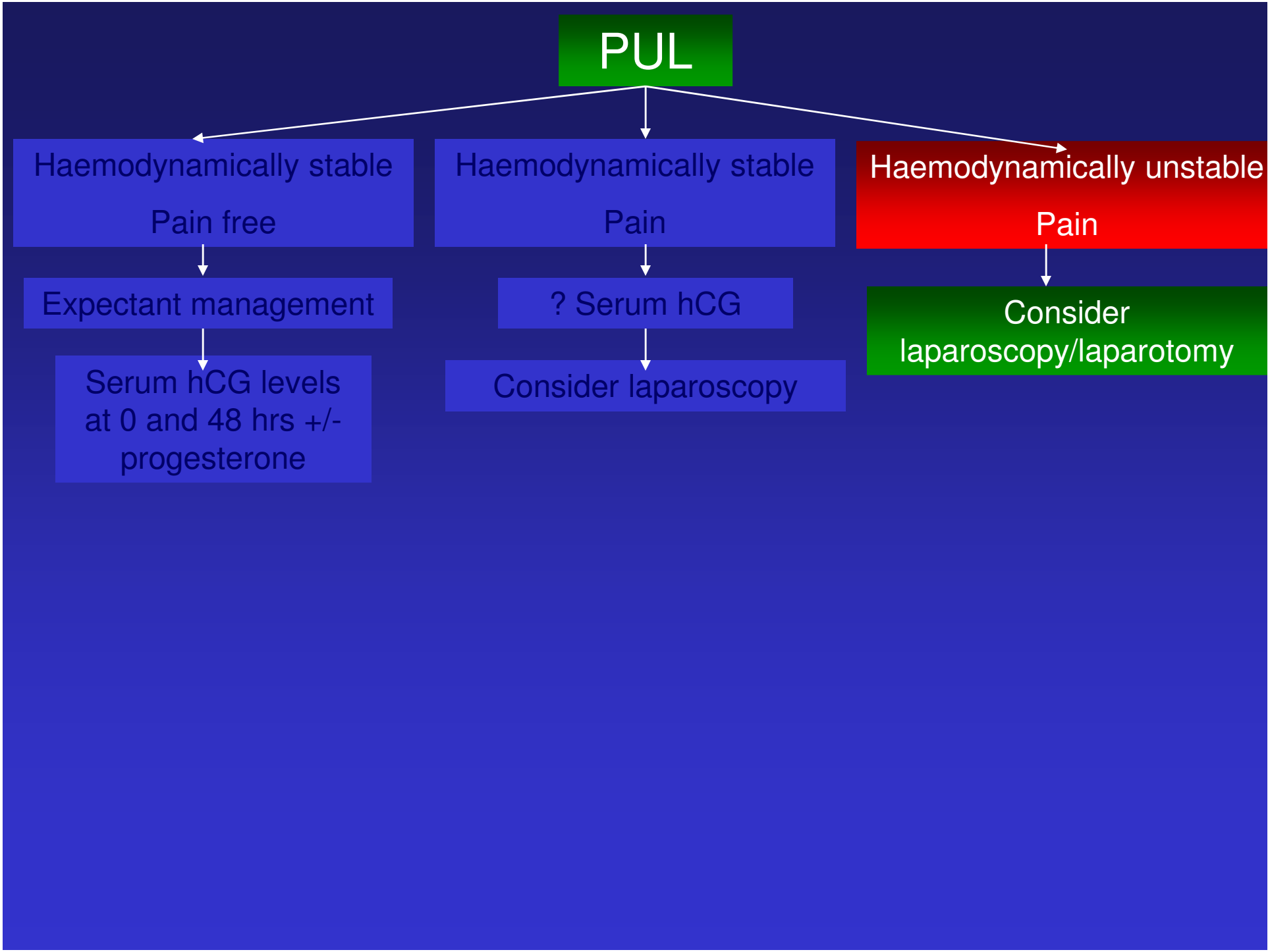
1. Assess clinical situation

- 5/40 Light PV spotting



- 7/40 Severe lower abdominal pain

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Pain free
Expectant management
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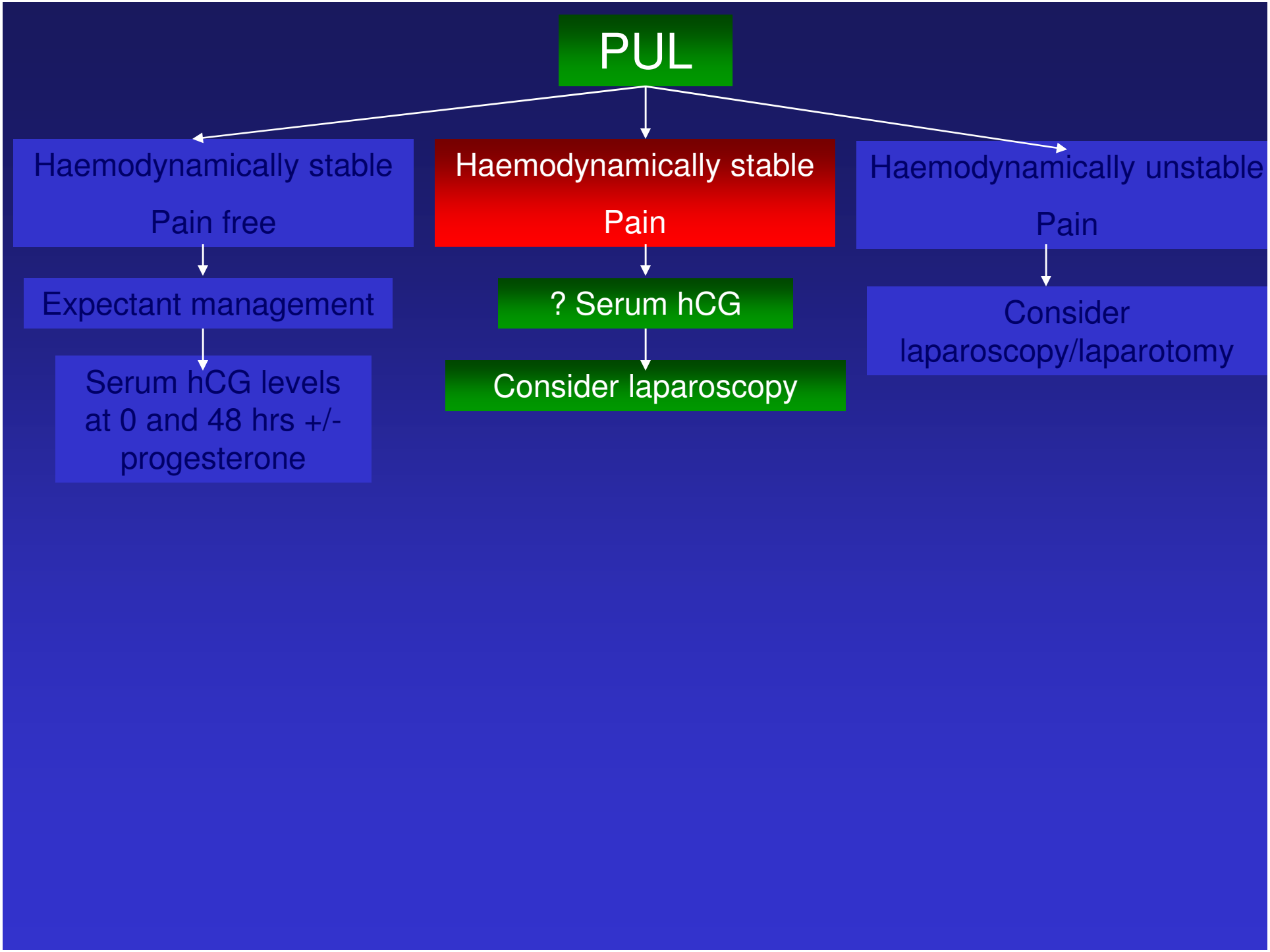
Pain
? Serum hCG
Consider laparoscopy
Haemodynamically unstable
Pain
Consider laparoscopy/laparotomy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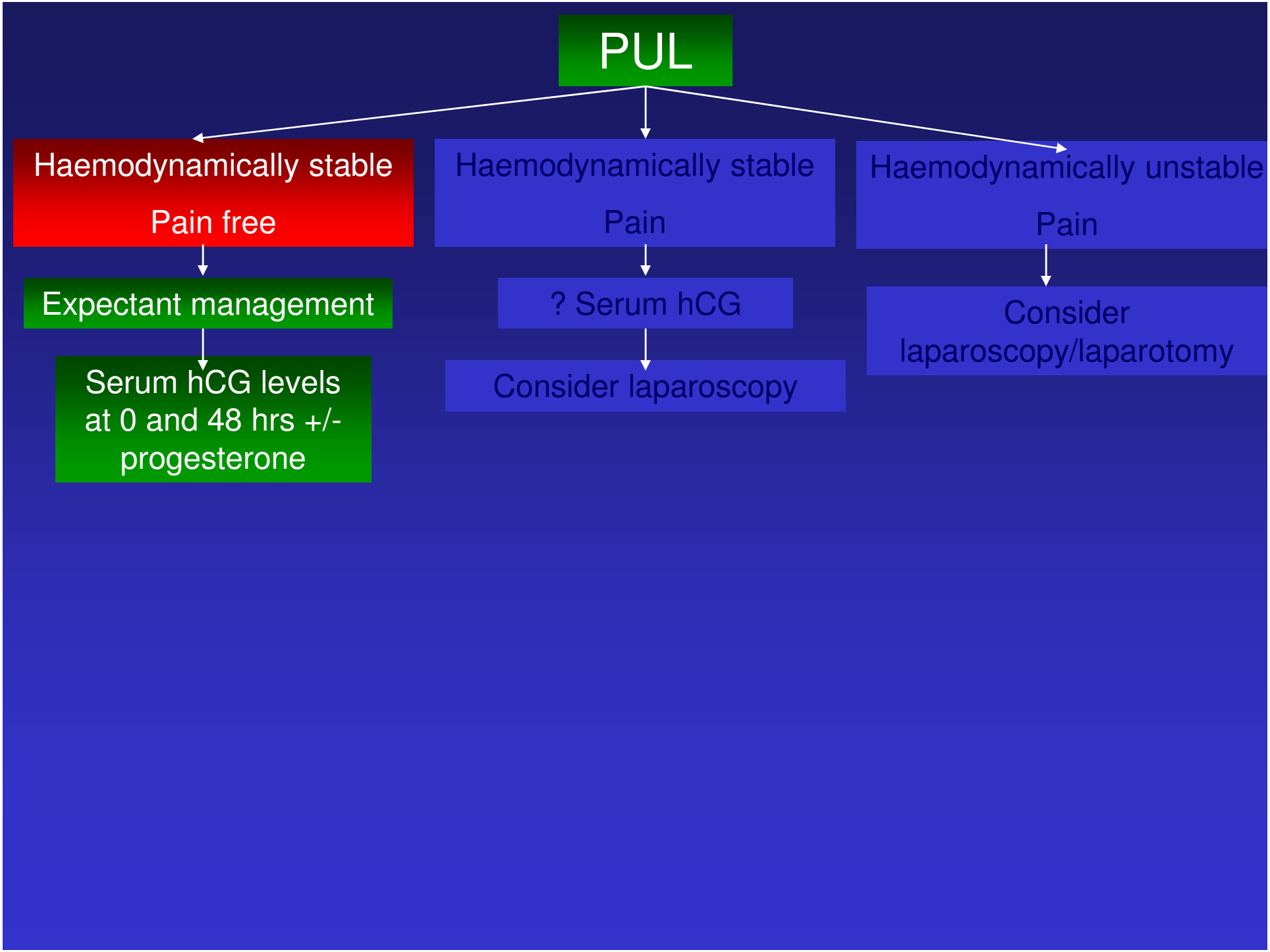
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Practical Advice - PULs

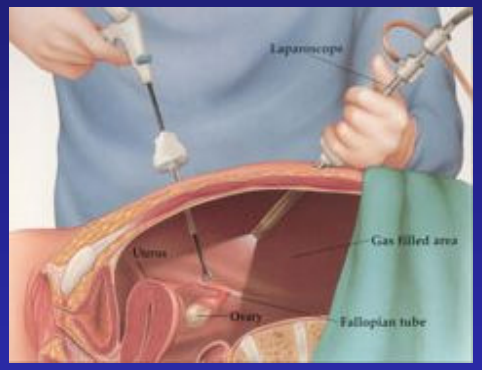
2. Expectant Management

- Safe for the majority of asymptomatic haemodynamically stable women with PULs
- No consensus on appropriate intervention rates
- Surgical intervention rates quoted as 0.3-11%

Practical Advice - PULs

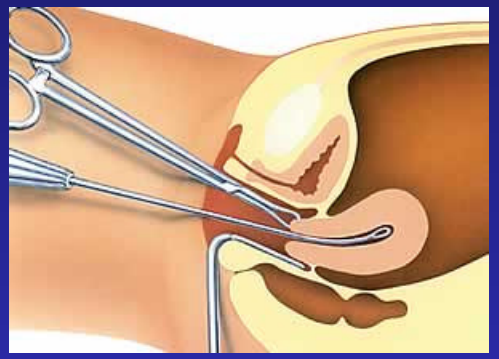
Surgical Intervention

Laparoscopy



- The combination of a positive pregnancy test and the absence of an IUP on TVS is an accepted indication for laparoscopy

Curettage

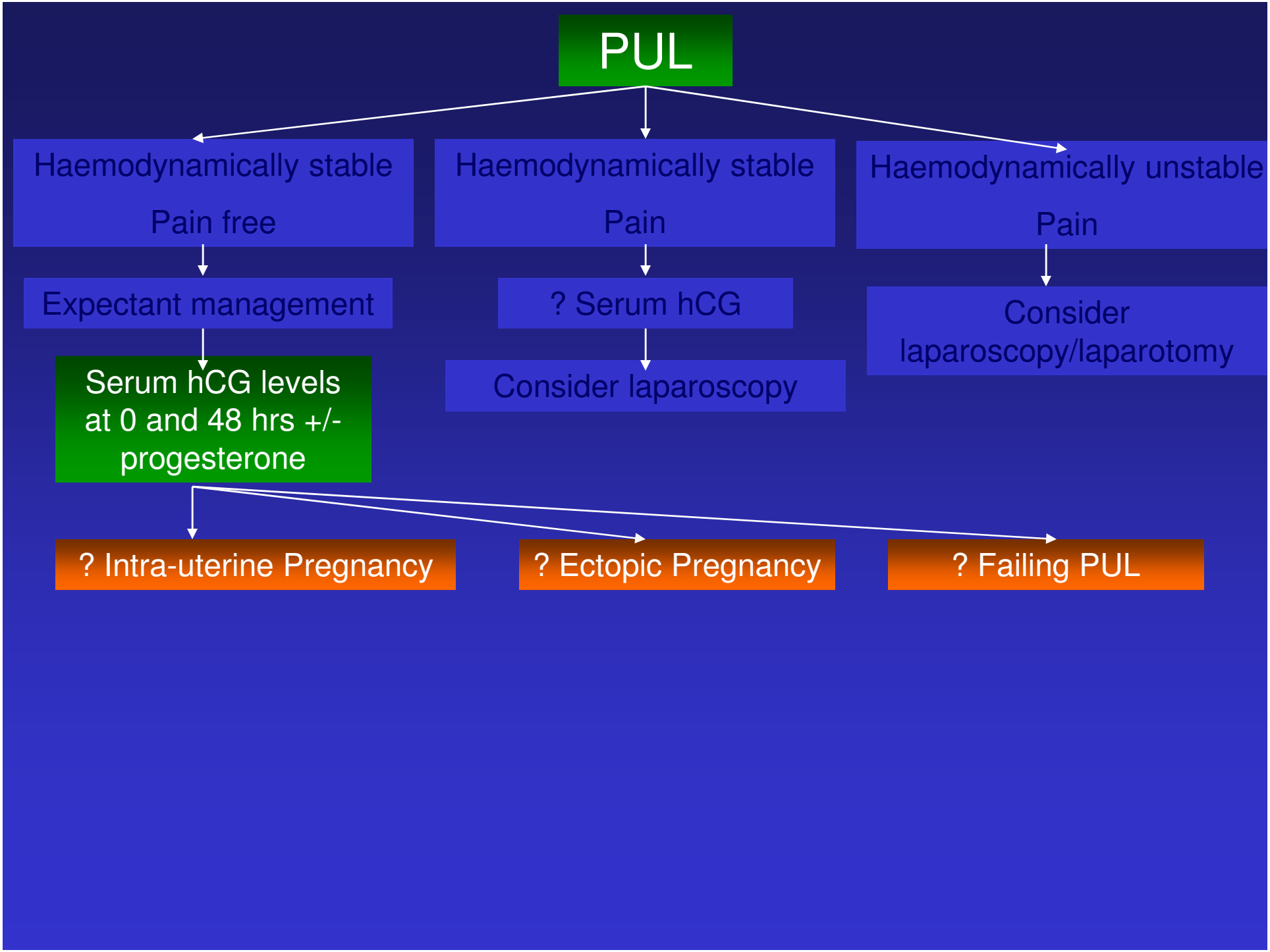


- Serial measurements of hCG and progesterone, TVS and uterine curettage have been combined into various diagnostic algorithms when a pregnancy cannot be seen on TVS

Practical Advice - PULs

3. Predicting outcome

- Hormones
  - Human chorionic gonadotrophin (hCG)
  - Progesterone
  - Other:
    - Creatine kinase
    - CA 125
    - Activin A
    - Inhibin A
- Mathematical Models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Serum hCG Levels

Single Levels

Serial Levels

Serum hCG Levels

Single Levels

Serial Levels

Discriminatory Zone

Serum hCG Levels

Single Levels

Serial Levels

Discriminatory Zone

- Developed with respect to transabdominal USS
- Lower levels of hCG used with TVS
- Using a single value of hCG in a PUL population is of limited value:
  - Many ectopic pregnancies have a low hCG
  - Clinicians may be falsely reassured

Serum hCG Levels

Single Levels

Serial Levels

↓

Change over 48hrs
(hCG ratio)

Intrauterine Pregnancies (IUPs)

- Kadar et al. (1981) first to describe the minimal rate of rise for an IUP to be 66% over 48hrs
- More recently minimal rise reported to be 53% *(Barnhart et al. 2004)*
- In clinical practice a more conservative cut-off of 35% has been suggested

Serum hCG Levels

Single Levels

Serial Levels

↓

Change over 48hrs
(hCG ratio)

Failing PULs

- A decline of 21-35% at 48 hours depending on initial hCG level (↑ levels at presentation –↑ rate of decrease) (*Barnhart et al. 2004*)
- An hCG decrease of >13% (hCG ratio < 0.87) has been shown to have a sensitivity of 92.7% and a specificity of 96.7% for the prediction of a failing PUL *(Condous et al., 2006)*

Serum hCG Levels

Single Levels

Serial Levels

↓

Change over 48hrs
(hCG ratio)

Ectopic Pregnancies (EPs)

- 'No single way to characterize the pattern of serum hCG behaviour' *(Silva et al., 2006)*
- hCG profile mimicked IUP in 21% and a spontaneous miscarriage in 8% *(Silva et al., 2006)*
- Sensitivity of 83% for EP when IUP excluded by hCG rise < 35% and failing PUL excluded by hCG decrease > 21-35% *(Seeber et al., 2006)*

Predicting outcome

- Hormones
  - Human chorionic gonadotrophin (hCG)
  - Progesterone
  - Other:
    - Creatine kinase
    - CA 125
    - Activin A
    - Inhibin A
- Mathematical Models

Serum Progesterone Levels

Serum Progesterone

< 20 nmol/L

PPV > 95% to predict pregnancy failure *(Banerjee et al., 2001)*

> 60 nmol/L

'Strongly' associated with viable pregnancies

Viable IUPs reported with levels < 16nmol/L

Discriminative capacity insufficient to diagnose ectopic pregnancy with certainty *(Mol et al., 1998)*

Good at predicting viability but not location

Practical Advice - PULs

3. Predicting outcome

- Hormones
  - Human chorionic gonadotrophin (hCG)
  - Progesterone
  - Other:
    - Creatine kinase
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- Mathematical Models

Mathematical models

- Prediction of failing PULs
  - Probability of spontaneous resolution $=1/(1+e^{-z})$
  - Where z = -2.20 - 0.15 * progesterone (nmol/L) + 3.36 * bleeding score - 0.0013 * serum β-hCG (IU/L) + 0.45 * endometrial thickness (mm) *(Banerjee et al., 2001)*
  - PPV > 95% for the prediction of pregnancy resolution
- Prediction of failing PULs, IUPs and EPs
  - Logistic regression models based on the hCG ratio (hCG 48hrs/hCG 0 hrs) *(Condous et al., 2004, Condous et al., 2007)*
  - Sensitivities >90% for the detection of EP

						true \ pred	Fail	IUP	EP	Tot		Sensitivity	Specifici	PPV	NPV
Prior cost fo each class					Total	Failing	66	1	26	93	Failing	70.97%	86.21%	######	65.79%
	1: Failing	2: IUP	3: Ectopic		Accurac	IUP	0	64	11	75	IUP	85.33%	73.33%	96.97%	67.54%
Cost(prior)	1.0	1.0	5.00		**77.90%**	EP	0	1	11	12	EP	91.67%	77.38%	22.92%	98.48%
						Tot	66	66	48	180					
	* hcgratio=hcg_48hr/hcg_0hr														

	input			Posterior Probability				Probability weighted by cost				Predicted			Real
ID	hcg_0hr	hcg_48hr	hcgratio*	Fail	IUP	EP		Failing	IUP	EP		Prob for	class		Outcom
1	1047	388	0.3706	0.94	0.00	0.05		0.7745	0.0007	0.2248		0.7745	1		1
2	350	750	2.1429	0.00	0.96	0.04		0.0013	0.8327	0.1661		0.8327	2		2
3															3
4															
5															

hCG ratio = hCG 48 hours / hCG 0 hours

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ID	hcg_0hr	hcg_48hr	hcgratio*	Fail	IUP	EP		Failing	IUP	EP		Prob for	class		Outcom
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2	350	750	2.1429	0.00	0.96	0.04		0.0013	0.8327	0.1661		0.8327	2		2
3	**590**														3
4															
5															

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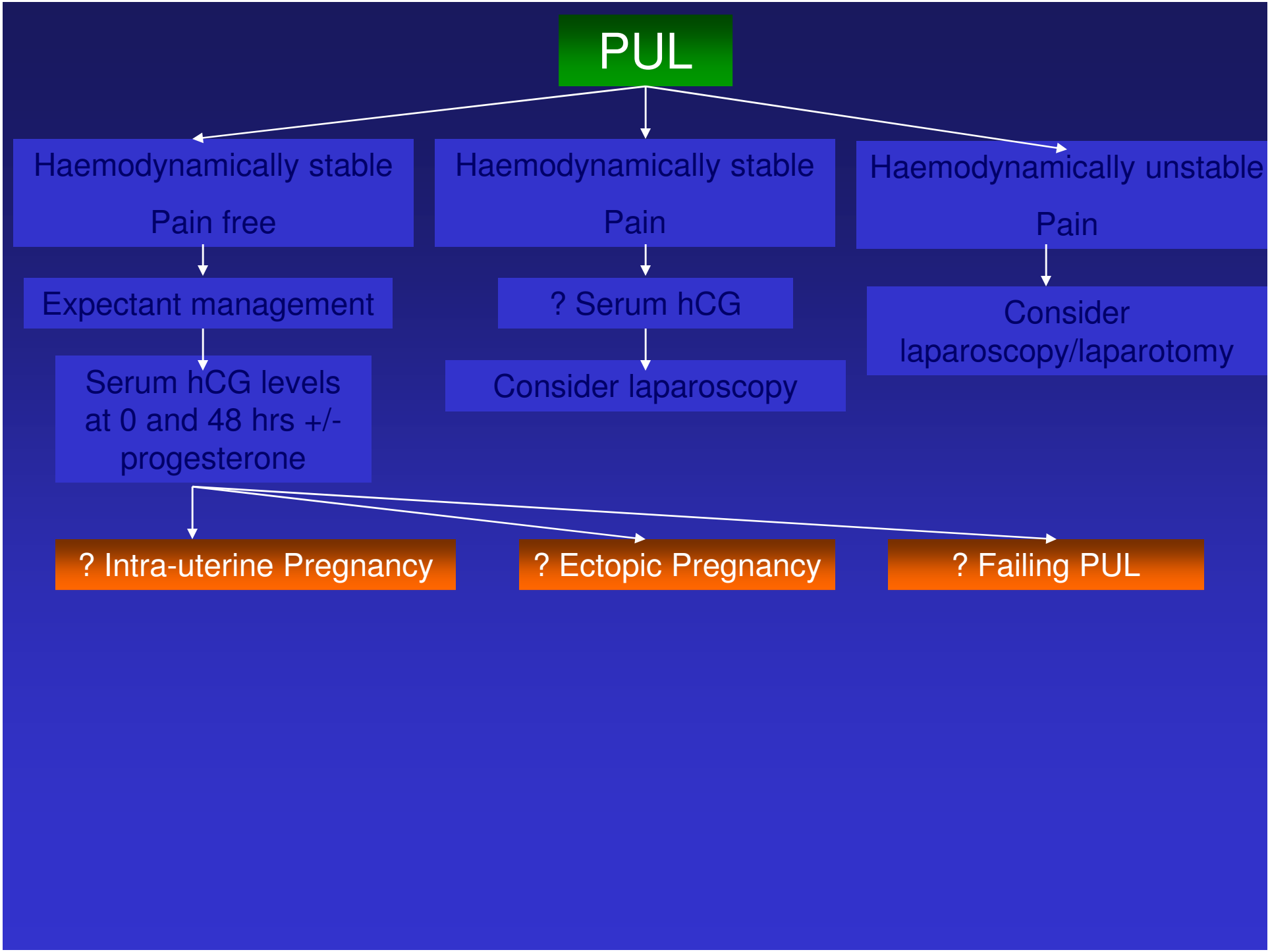
3	590	**700**	1.1864	0.42	0.18	0.40		0.1593	0.0692	0.7716		0.7716	**3**		
4															
5															

hCG ratio = hCG 48 hours / hCG 0 hours

Practical Advice - PULs

4. Follow-up

- Methods?
- Timing of visits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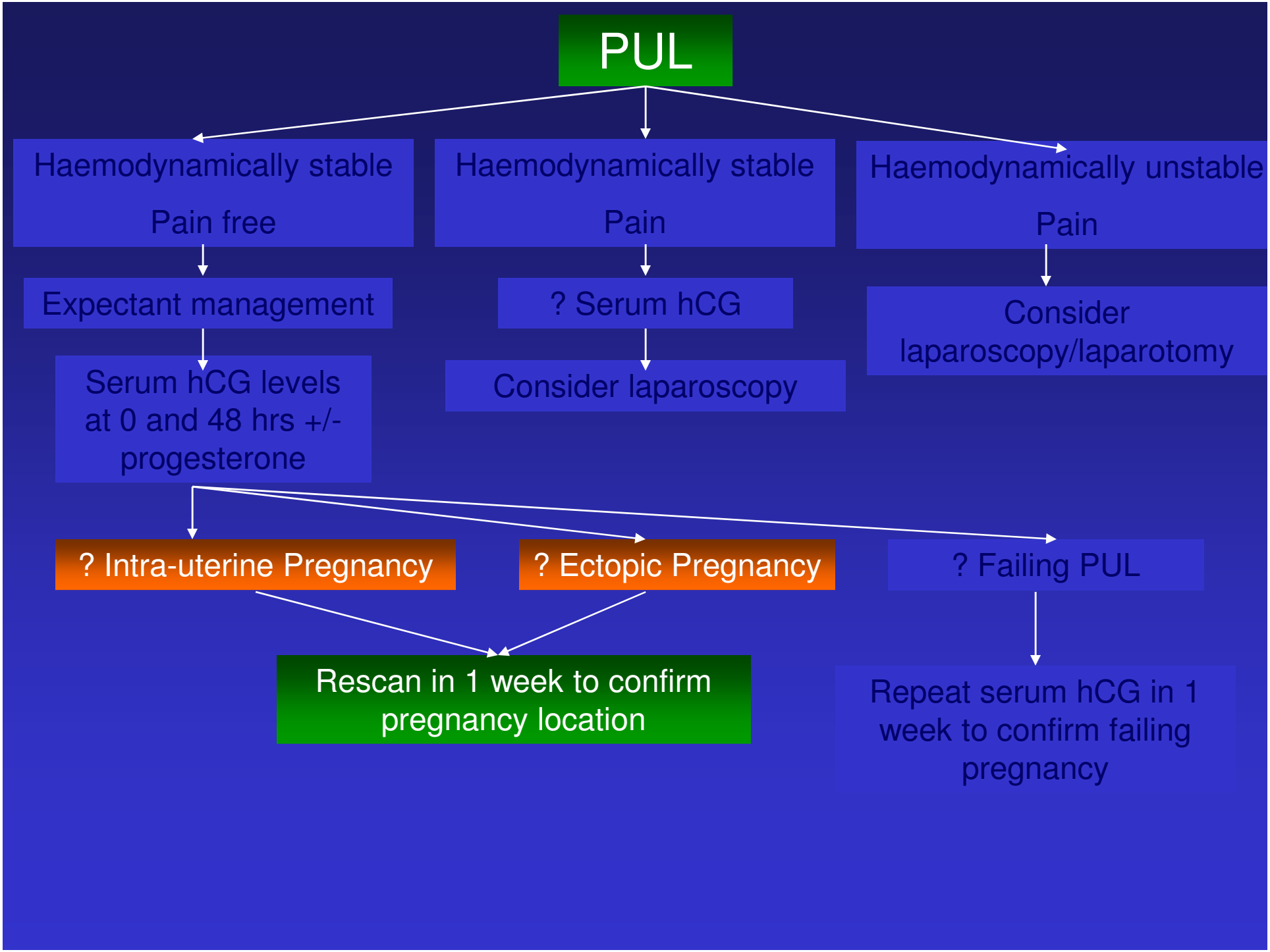
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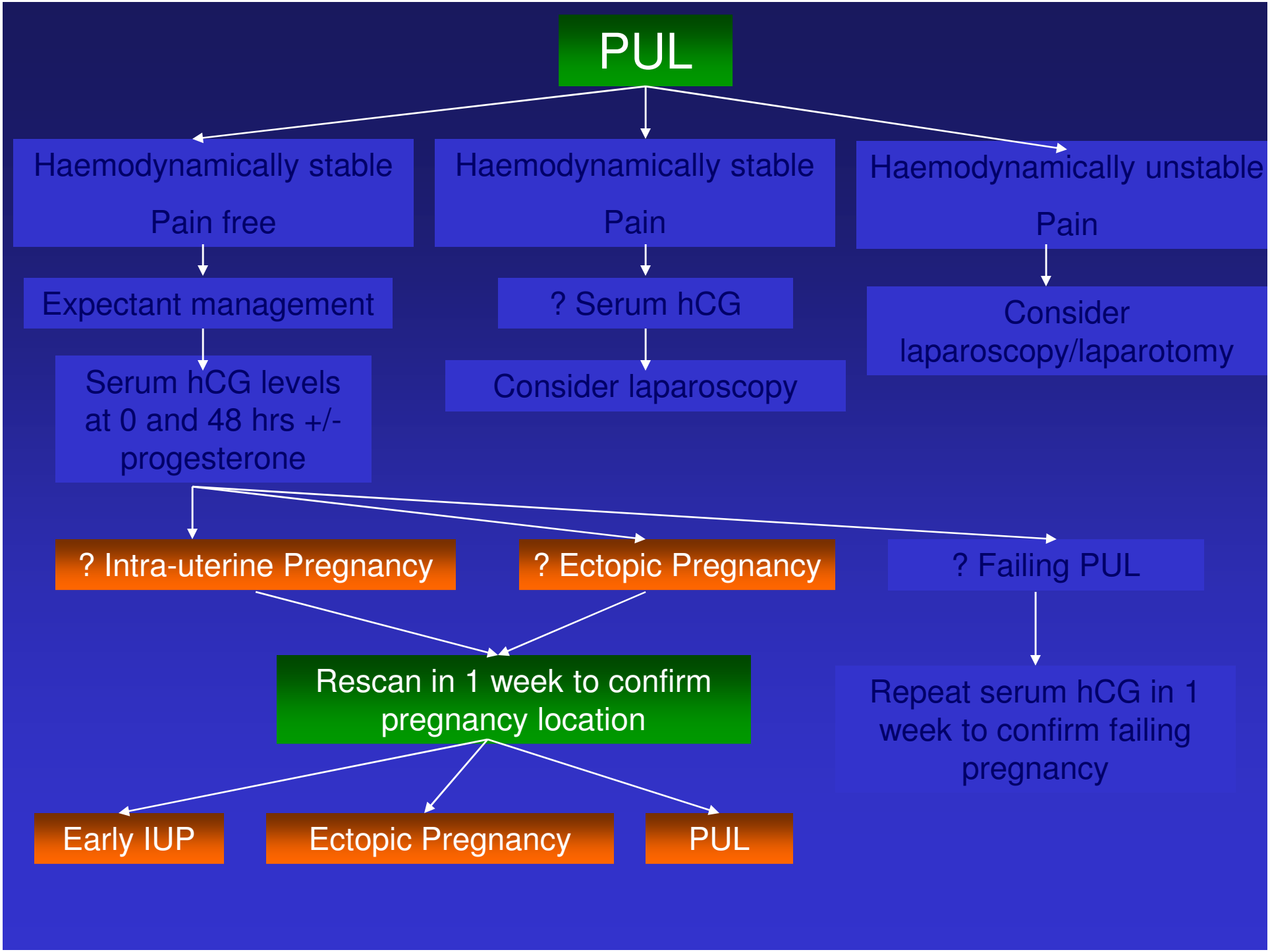
Rescan in 1 week to confirm pregnancy location
Repeat serum hCG in 1 week to confirm failing pregnancy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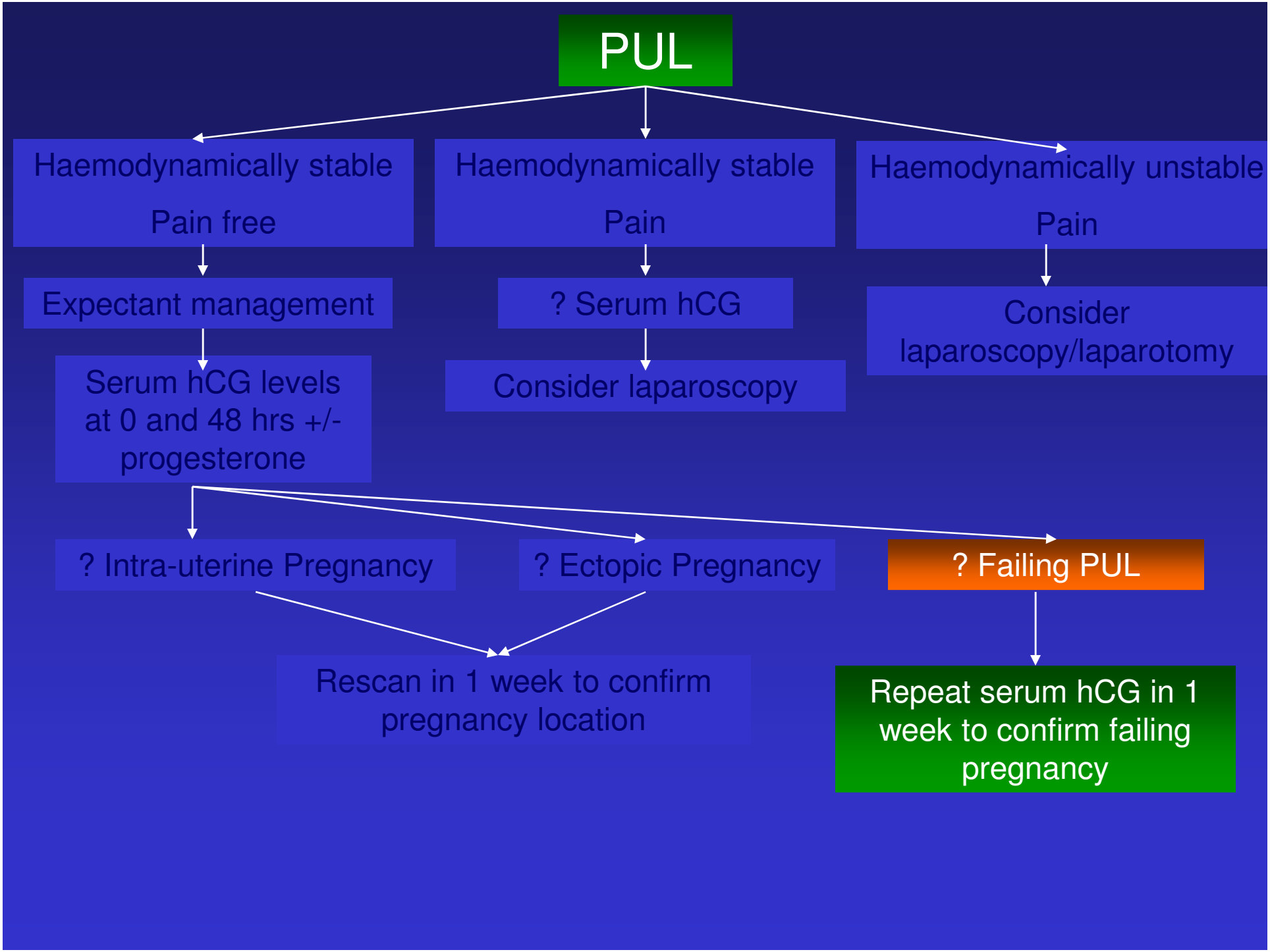
Early IUP
Ectopic Pregnancy
PUL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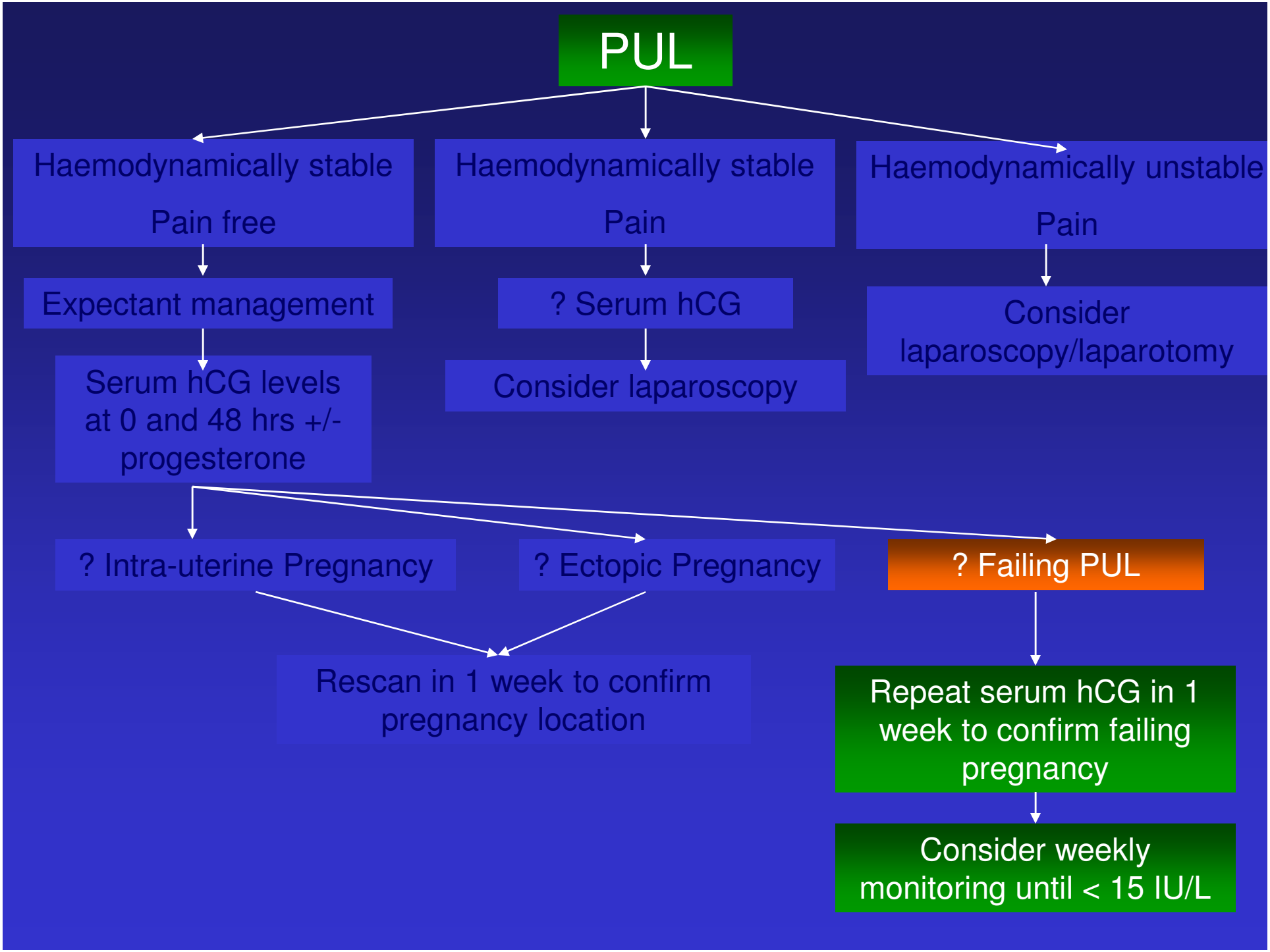
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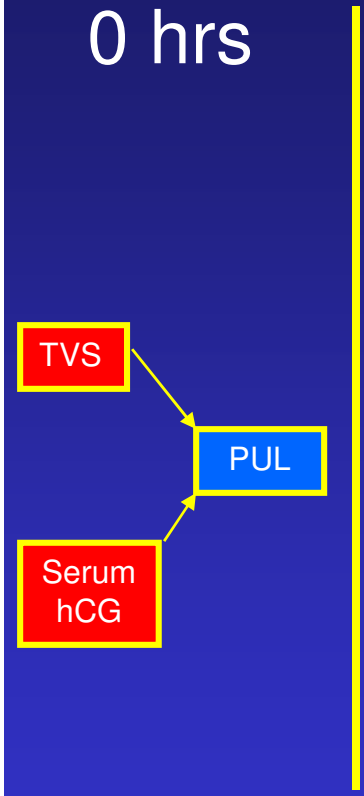
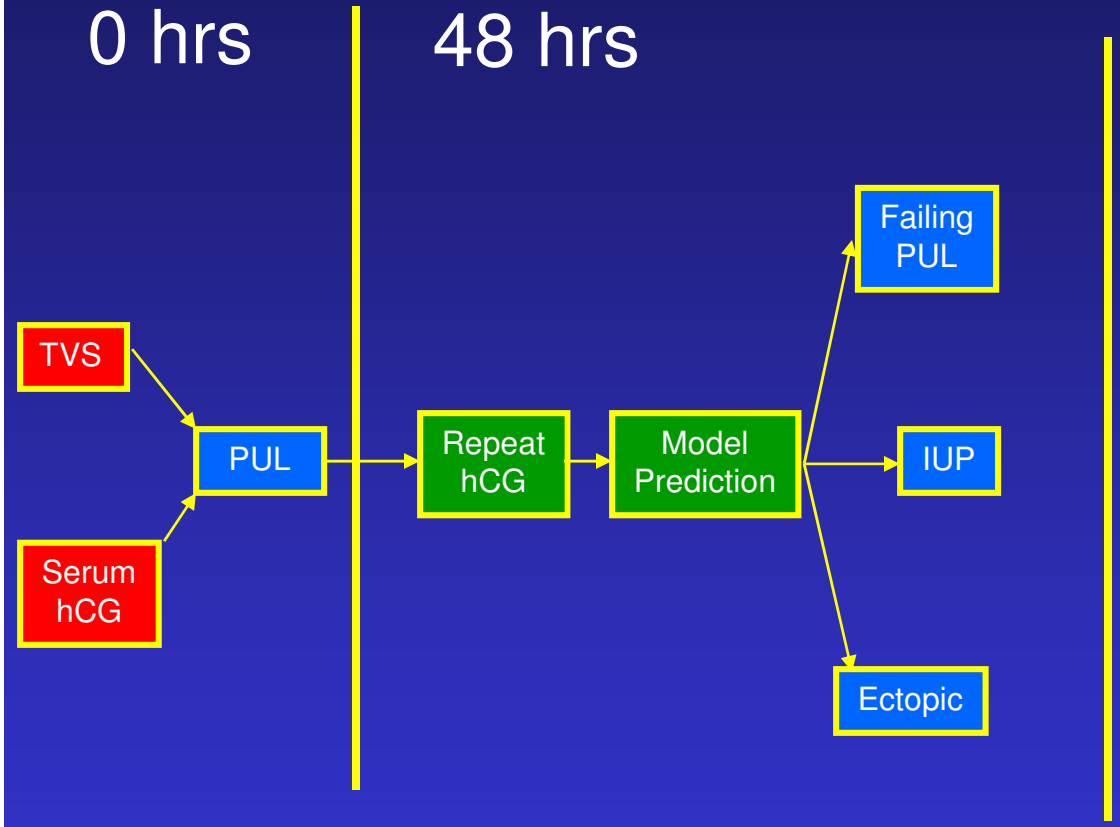
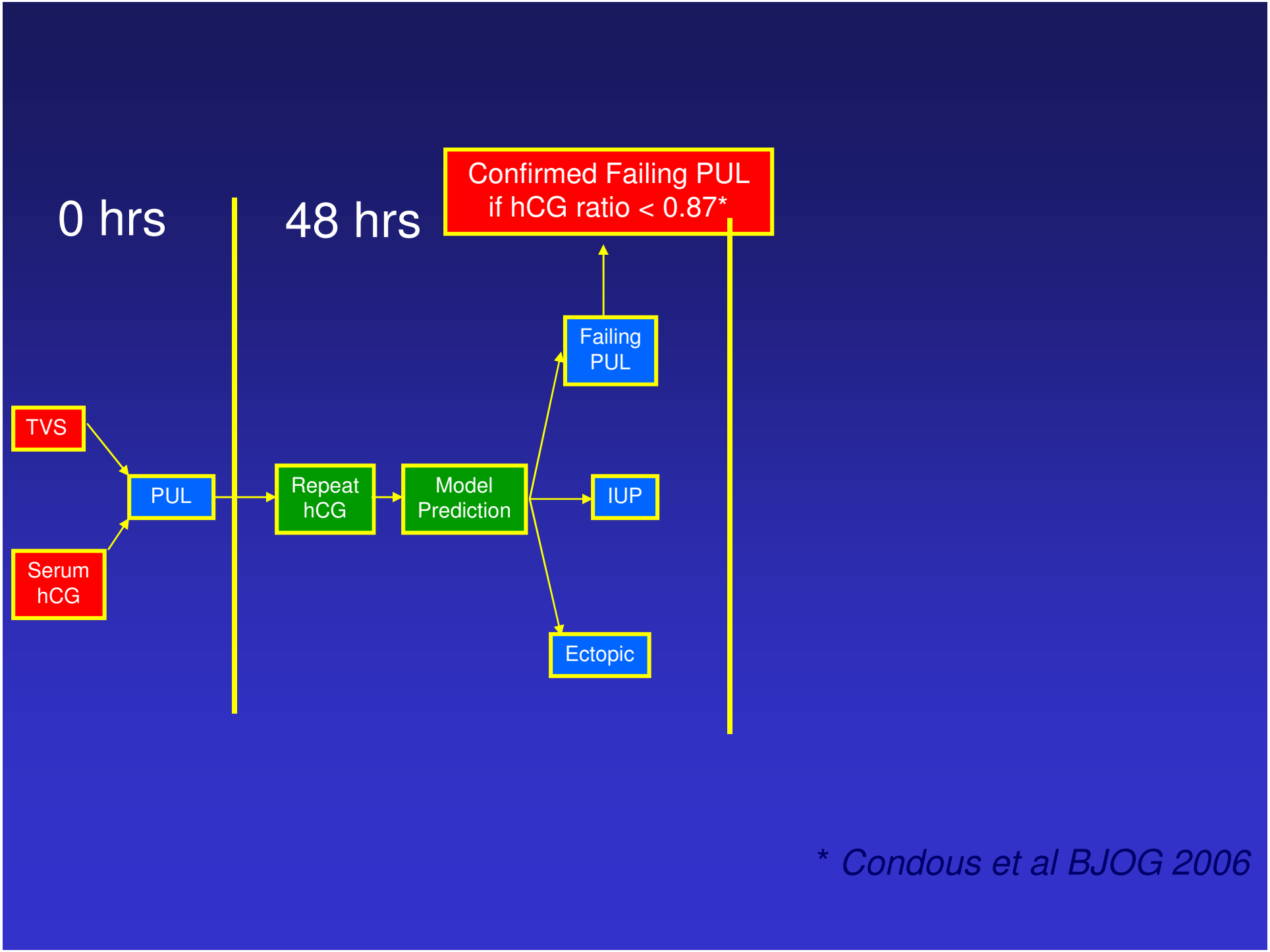
Rescan in 1 week to confirm pregnancy location
Repeat serum hCG in 1 week to confirm failing pregnancy
Consider weekly monitoring until < 15 IU/L

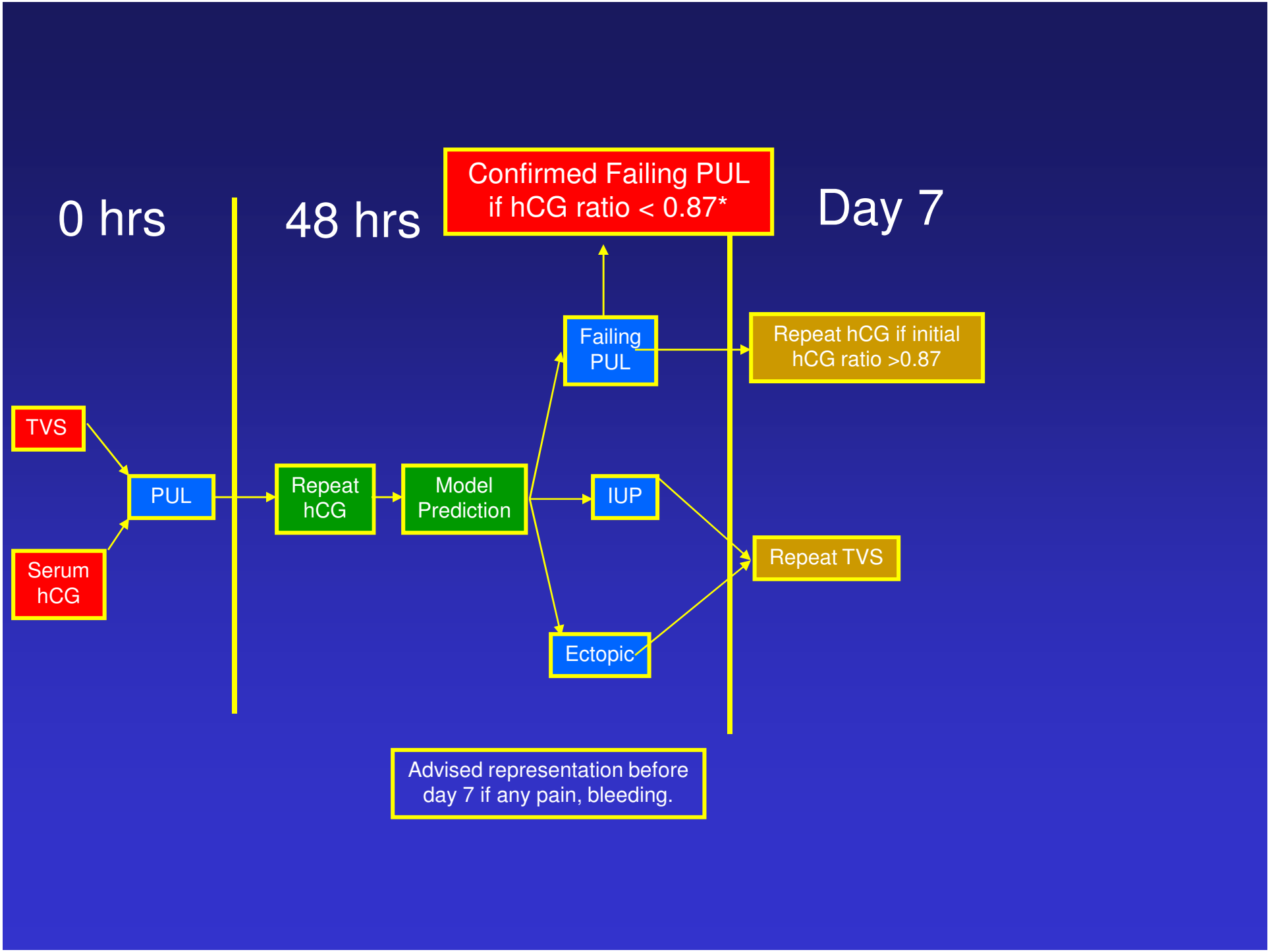
Rationalizing the follow-up of PULs *Hum Reprod 2007; 22:1744-50*

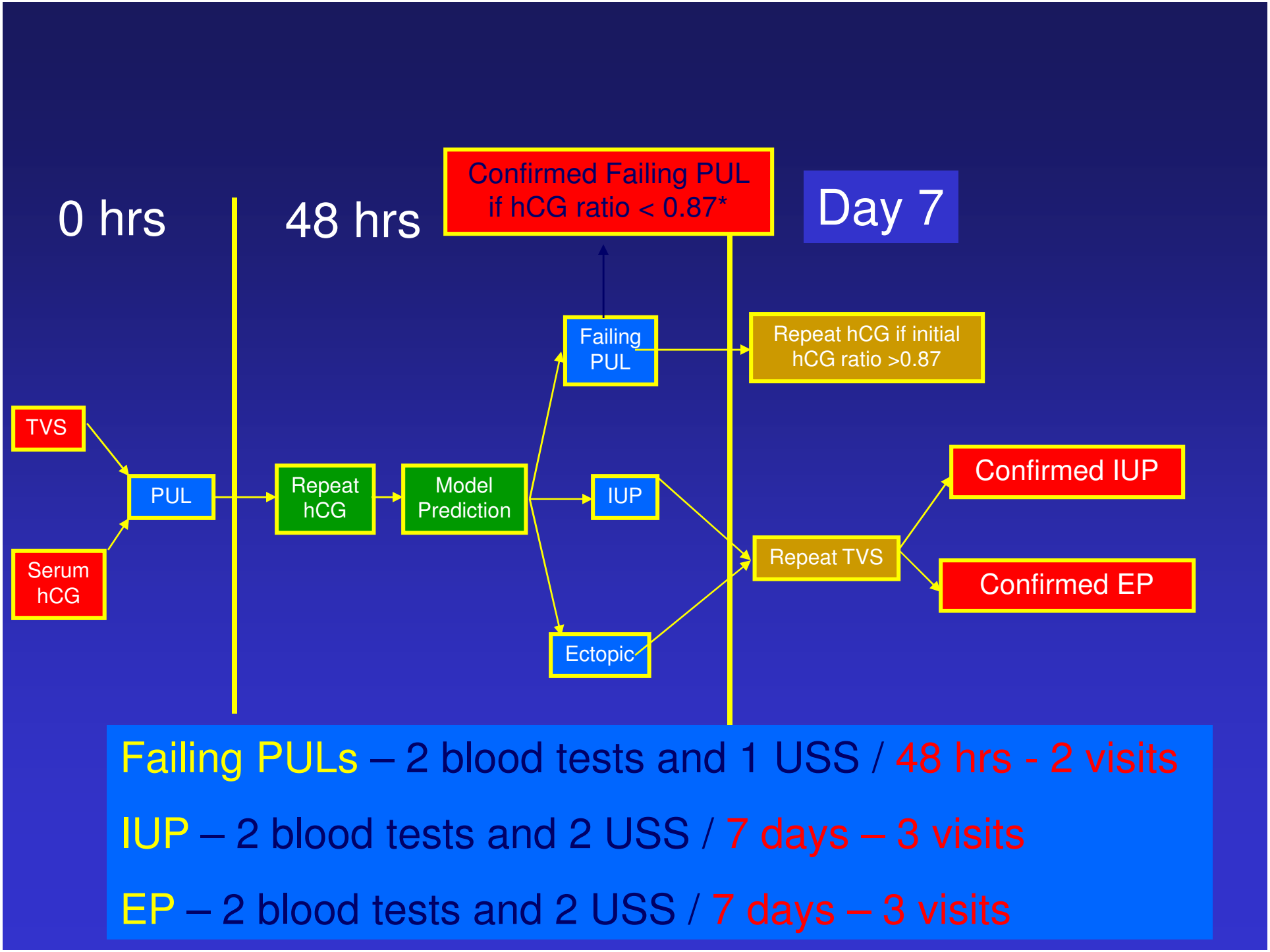



0 hrs
48 hrs
TVS
Serum hCG
PUL
Repeat hCG
Model Prediction
Failing PUL
IUP
Ectopic



** Condous et al BJOG 2006*

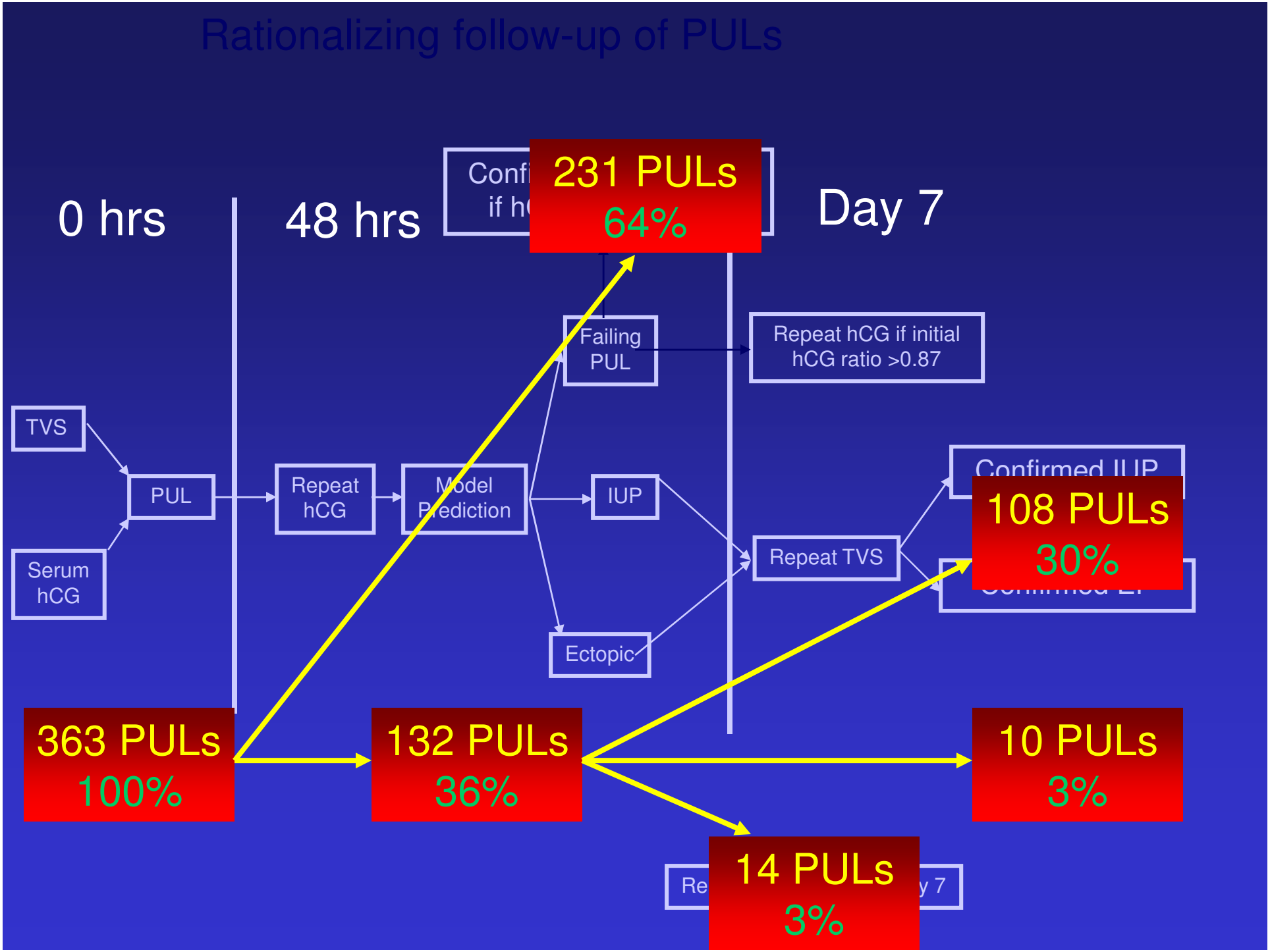

0 hrs
48 hrs
Day 7
Confirmed Failing PUL if hCG ratio < 0.87*
Failing PUL
Repeat hCG if initial hCG ratio >0.87
TVS
PUL
Serum hCG
Repeat hCG
Model Prediction
IUP
Repeat TVS
Ectopic
Advised representation before day 7 if any pain, bleeding.

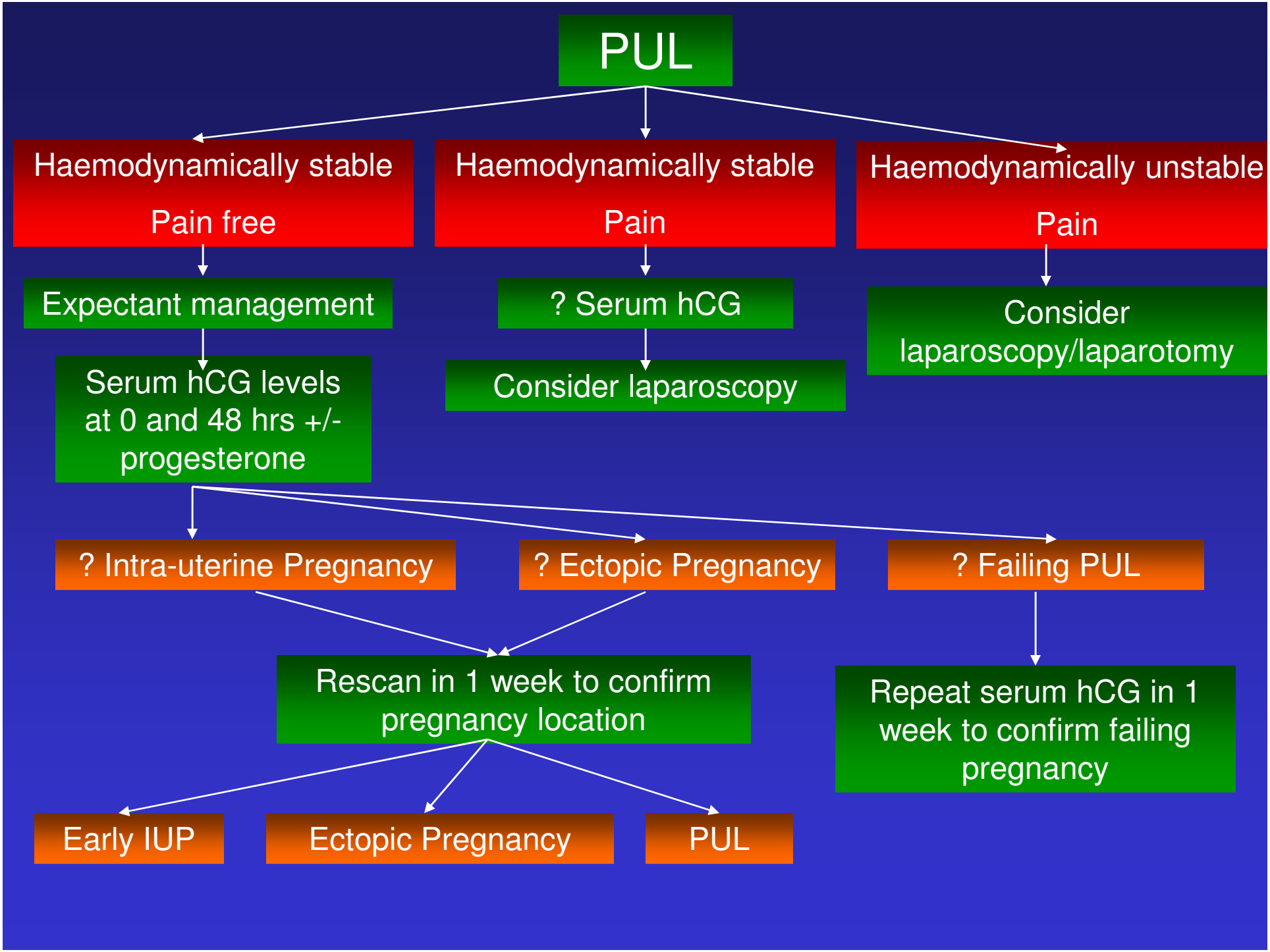


Failing PULs – 2 blood tests and 1 USS / 48 hrs - 2 visits

IUP – 2 blood tests and 2 USS / 7 days – 3 visits

EP – 2 blood tests and 2 USS / 7 days – 3 visits


Rationalizing follow-up of PULs
0 hrs
48 hrs
Day 7
231 PULs
64%
Failing PUL
Repeat hCG if initial hCG ratio >0.87
TVS
Serum hCG
PUL
Repeat hCG
Model Prediction
IUP
Ectopic
Repeat TVS
108 PULs
30%
363 PULs
100%
132 PULs
36%
10 PULs
3%
14 PULs
3%


PUL
Haemodynamically stable
Pain free
Haemodynamically stable
Pain
Haemodynamically unstable
Pain
Expectant management
? Serum hCG
Consider laparoscopy/laparotomy
Serum hCG levels at 0 and 48 hrs +/- progesterone
Consider laparoscopy
? Intra-uterine Pregnancy
? Ectopic Pregnancy
? Failing PUL
Rescan in 1 week to confirm pregnancy location
Repeat serum hCG in 1 week to confirm failing pregnancy
Early IUP
Ectopic Pregnancy
PUL

Summary

1. Expectant management suitable for majority of women
2. No consensus on appropriate intervention rates but no routine role for curettage
3. Serum hCG and progesterone levels useful, but no role for single hCG measurement
4. Mathematical models may be useful
5. Follow-up visits may be rationalised using management algorithms

Thank you