Evaluating the Literature on Pre-operative Androgen Stimulation for Hypospadias Repair Using the Fragility Index

Which Can We Trust – Randomized Controlled Trials or Observational Studies?

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Pre-operative Androgen Stimulation (PAS) in Hypospadias Repair

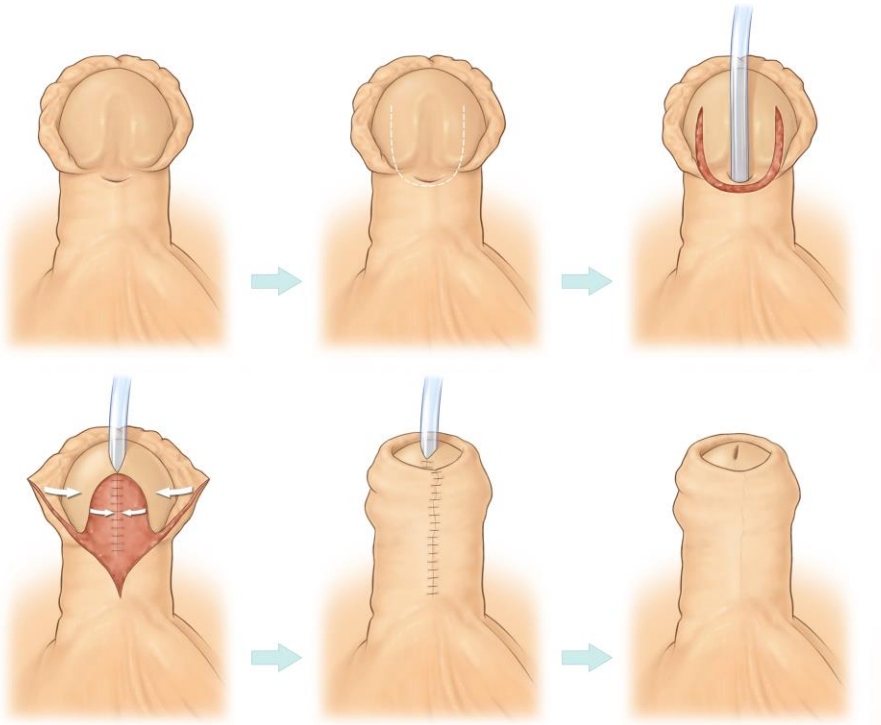
Why?

- The aim of hypospadias surgery is to reconstruct the urethra to the tip of the glans while achieving an acceptable functional and cosmetic result

Controversy surrounding use of PAS

\+ Promote phallic growth → **easier correction and theoretically better surgical outcomes**

\- Repressive effect on healing process leading to **increased risk of post-operative complications**



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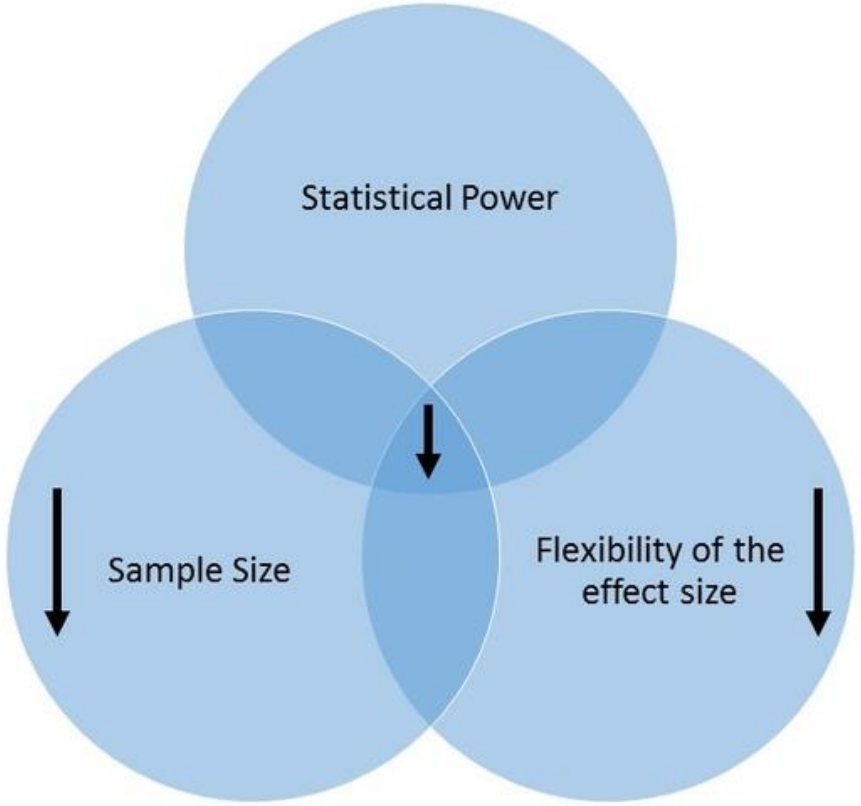
Pre-operative Androgen Stimulation (PAS) in Hypospadias Repair

Problem?

- Current hypospadias literature involving PAS suffers from small sample sizes and therefore, are underpowered

→ Small variations in results represent a large proportion of the sample and may change statistical significance

= unreliable results



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The Fragility Index by McMaster University

Fragility Index (FI): number of additional events needed to occur in either the control or experimental group in order to lose statistical significance ($p > 0.05$) as a **measure of statistical robustness** by Walsh et al, 2014.

Let's consider an example…

RCT #1	Myocardial infarction			
		Yes	No	P-value
Drug A	Yes	1	99	0.02
	No	9	91	

Sample size = 200 patients

RR = 0.11 (0.01 — 0.86)

RCT #2	Myocardial infarction			
		Yes	No	P-value
Drug A	Yes	200	3800	0.02
	No	250	3750	

Sample size = 8000 patients

RR = 0.80 (0.67 — 0.96)

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RCT #1	Myocardial infarction		
	Yes	No	P-value
Drug A	Yes	1 (+1)	99 (-1)	0.02
	No	9	91	

RCT #1	Myocardial infarction		
	Yes	No	P-value
Drug A	Yes	2	98	0.06
	No	9	91	

FI of RCT #1 = 1

RCT #2	Myocardial infarction		
	Yes	No	P-value
Drug A	Yes	200 (+9)	3800 (-9)	0.02
	No	250	3750	

RCT #2	Myocardial infarction		
	Yes	No	P-value
Drug A	Yes	209	3791	0.06
	No	250	3750	

FI of RCT #2 = 9

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Methods

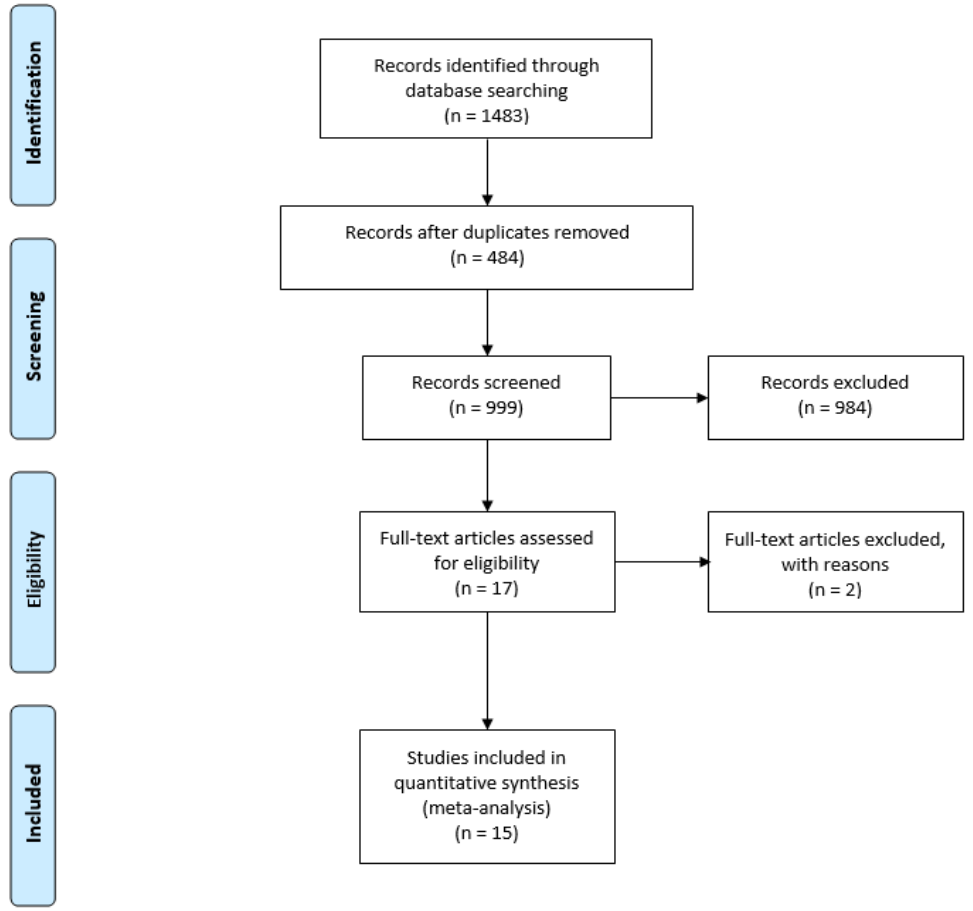
- MEDLINE and Embase database search
- ESPU and SPU abstracts were hand searched

Inclusion Criteria:

1. At least two (2) groups comparing pre-operative testosterone, androgen, or DHT use to no hormone use in the context of hypospadias repair
2. Results including difference in overall or specific complications of hypospadias repair*
3. Age between 0 – 18
4. Publication date between 1990 – 2019

*Note: Complications were defined as: fistula, stricture/stenosis, diverticula, and dehiscence

- FI, relative risk (RR), 95% confidence intervals (CI), corresponding p-values, and post-hoc power were calculated



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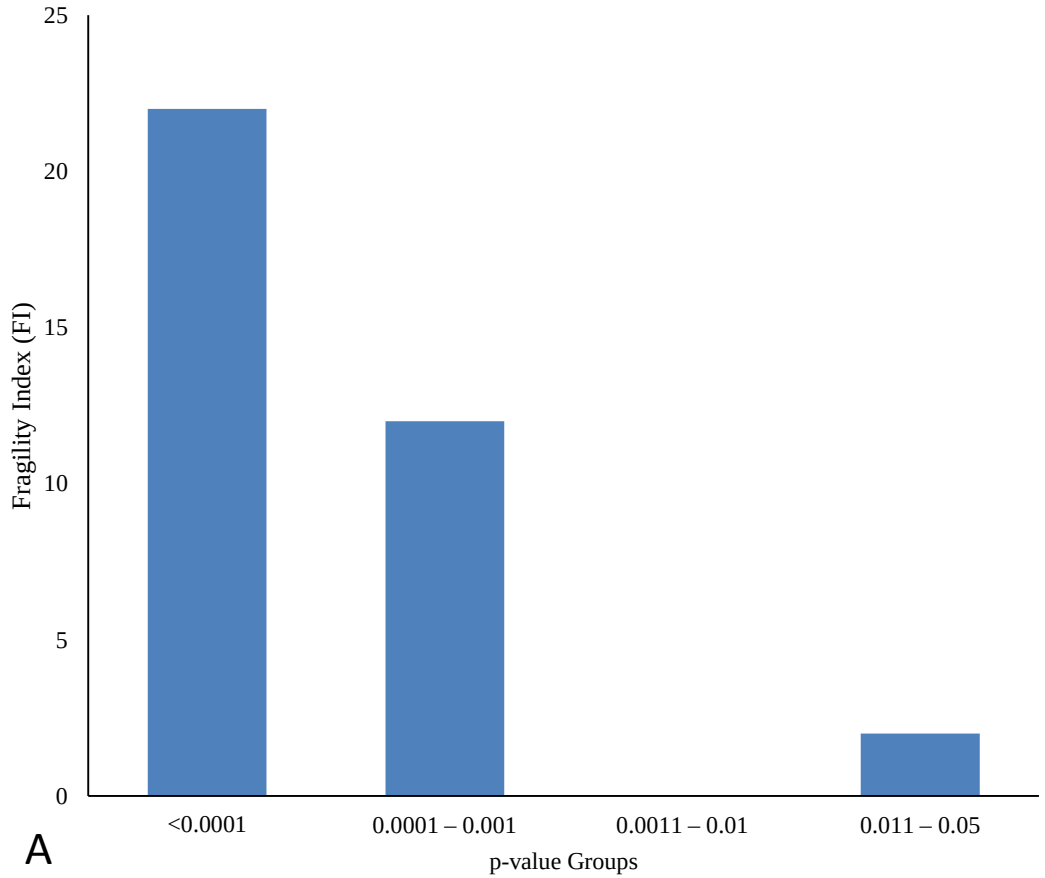
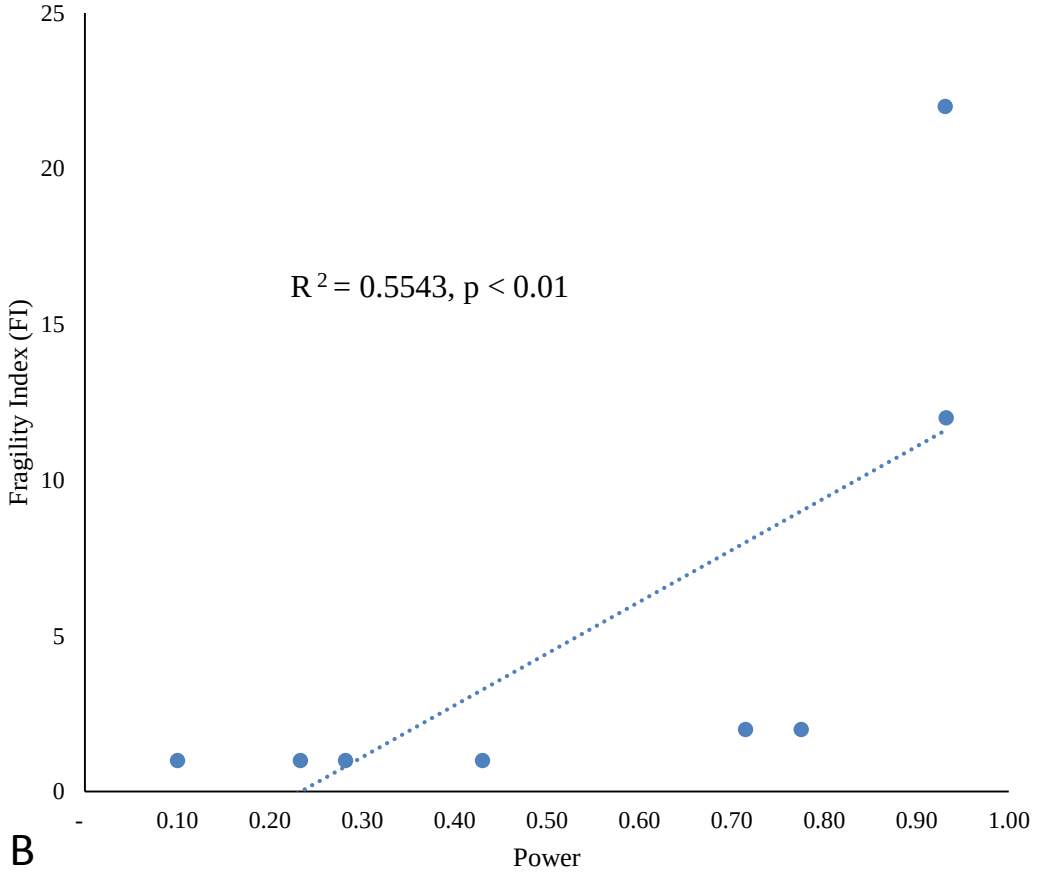
Results

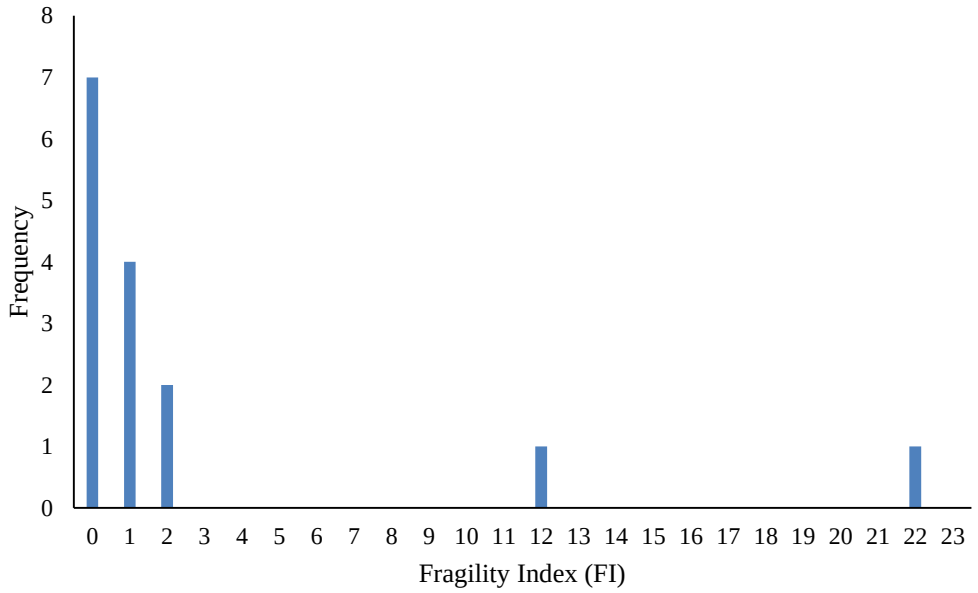

25
20
15
10
5
0
Fragility Index (FI)
<0.0001
0.0001 – 0.001
0.0011 – 0.01
0.011 – 0.05
p-value Groups

A

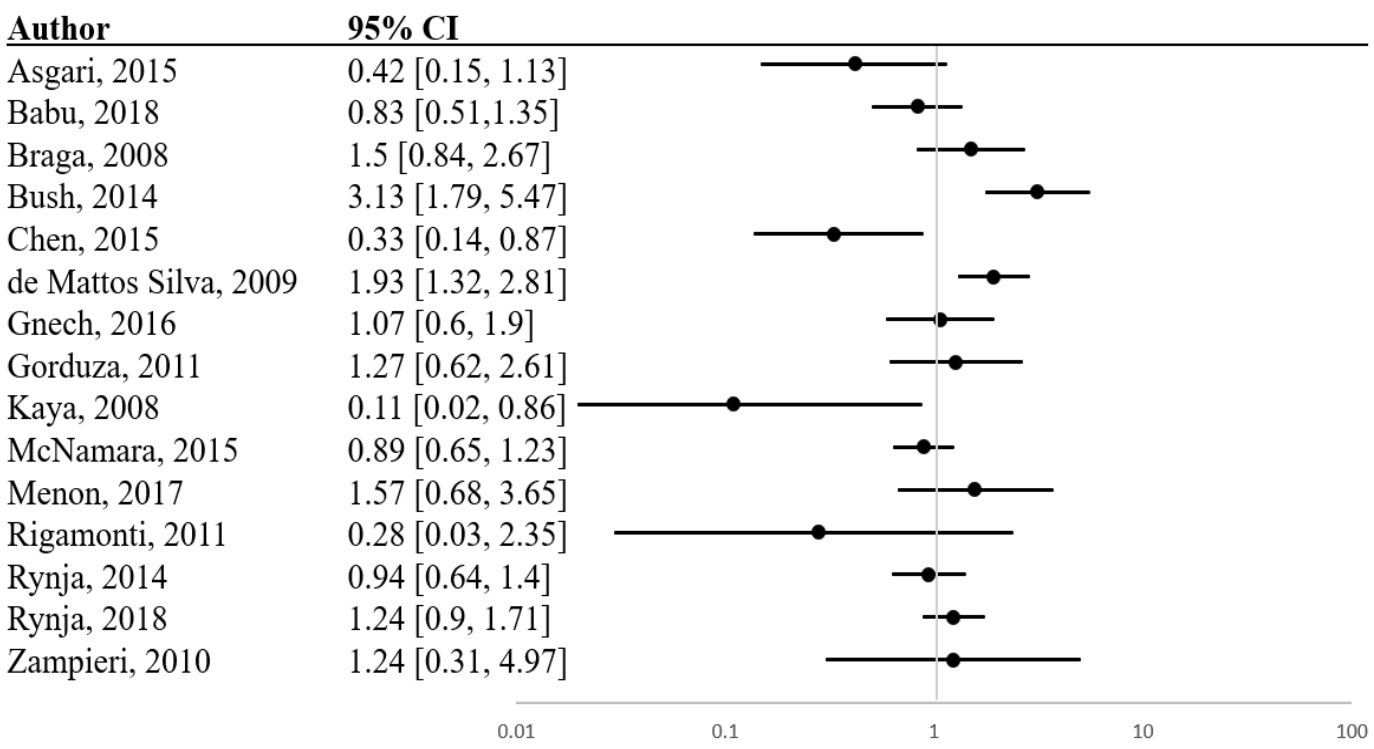

25
20
15
10
5
0
Fragility Index (FI)
R 2 = 0.5543, p < 0.01
-
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
Power

B

Results



Mean FI of observational studies similar to that of RCTs (3.7 vs. 1, p = 0.44)



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Discussion

In General

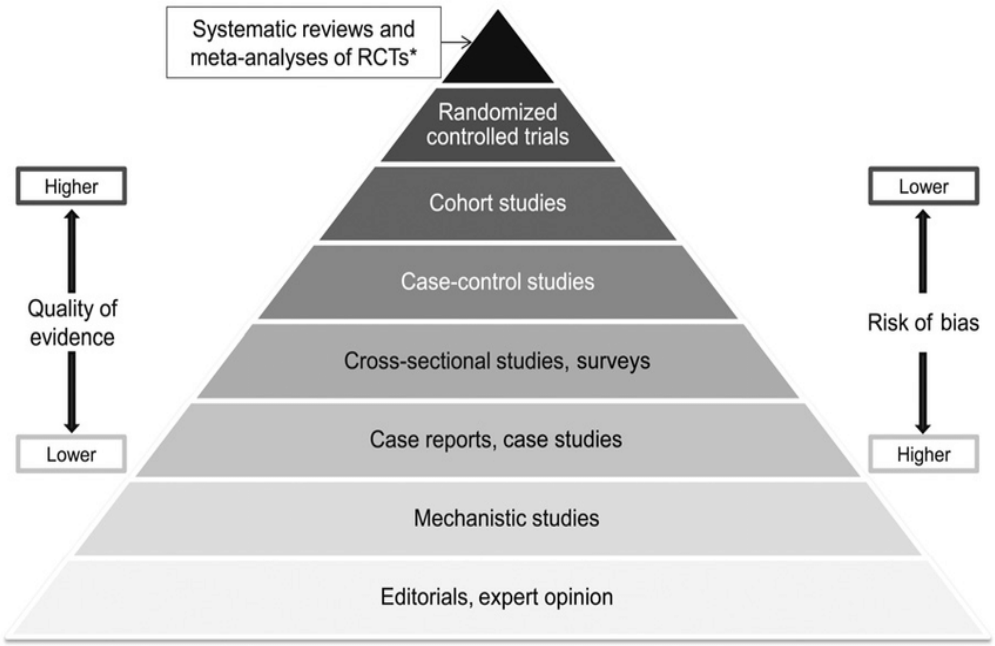
- FI was found to be positively correlated with power and negatively with p-value – **indicating ability to assess robustness of study results**

RCTs

- Weak protective effect or no harmful influence of PAS on complication rate
- Small FI → not robust results

Observational Studies

- Strong statistical significance based on power, p-value, and FI towards harmful effects of PAS on complication rate
- Methodological issues with observational studies



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Future Directions

1. FI is an important parameter to consider when appraising hypospadias literature as a measure of the robustness of the study results
2. PAS literature is insufficient from a statistical or methodological standpoint to draw strong conclusions

Caution is warranted before changing clinical practice!

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