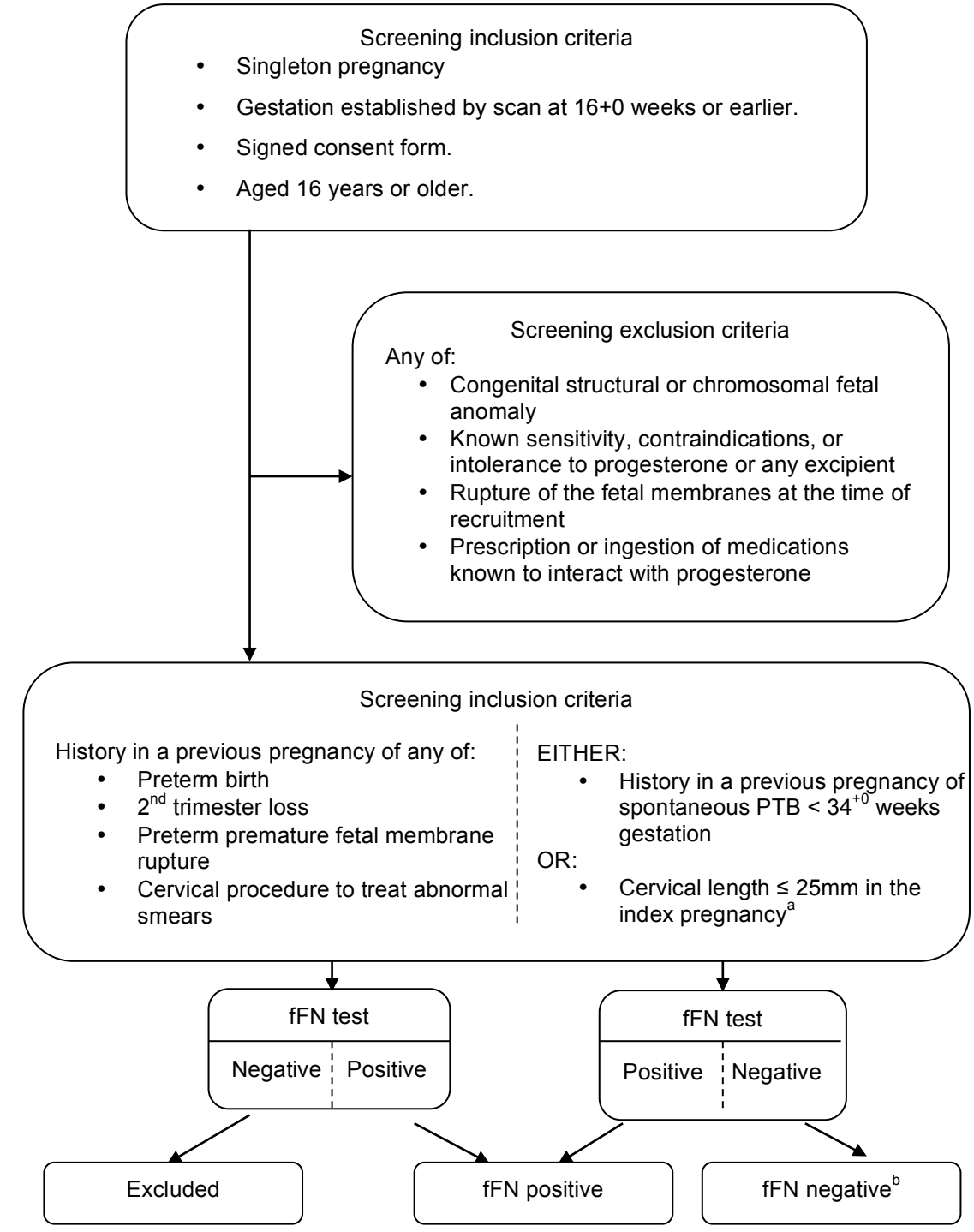
THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

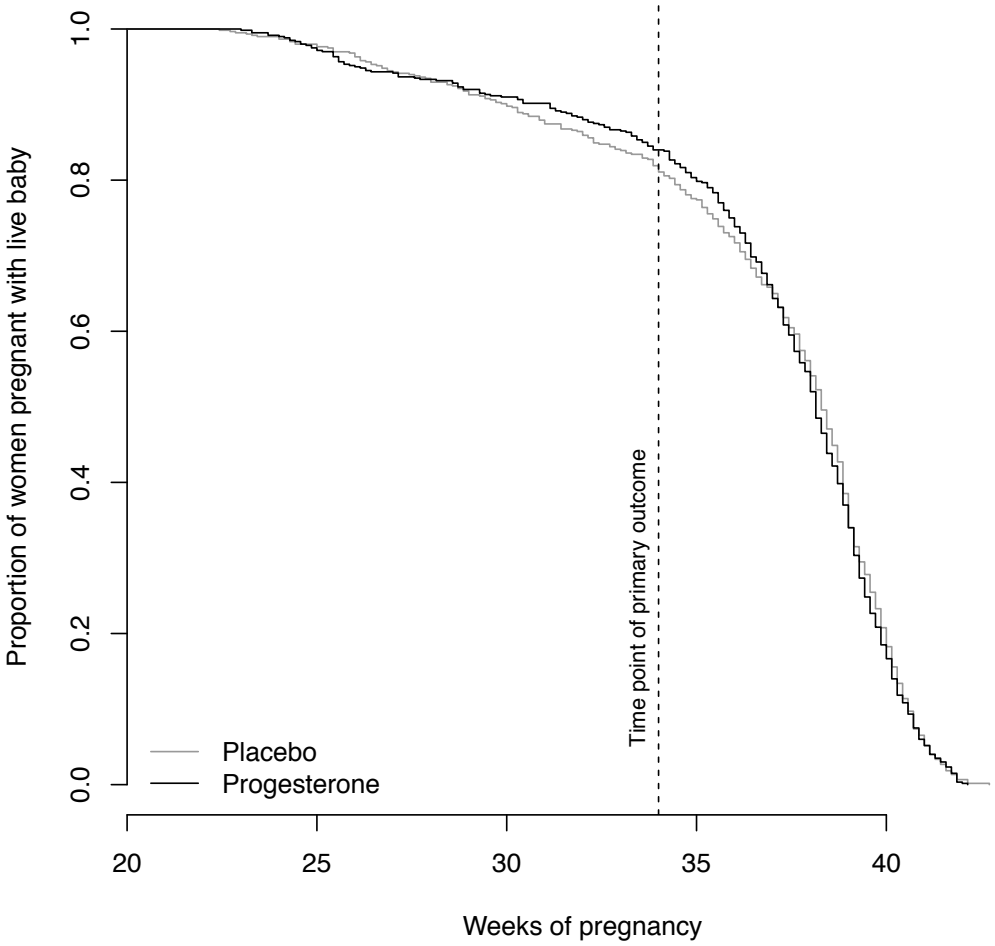
Supplement to: Norman JE, Marlow N, Messow C-M, et al, for the OPPTIMUM study group. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. *Lancet* 2016; published online Feb 23. http://dx.doi.org/10.1016/S0140-6736(16)00350-0.

Supplementary Figure 1: Eligibility and allocation to fFN (fibronectin) positive and ffN negative groups in the treatment phase.



[a]Measured at between 18^{+0} and 24^{+0} weeks gestation
[b]Eligible from September 2010 onwards

Supplementary Figure 2 Survival curve for gestation at delivery



Supplementary Table 1.

Characteristics of those participants for whom a childhood outcome was and was not available.

Characteristic	**No childhood outcome available (N=356)**	**Childhood outcome available (N=869)**
General		
Age - years	29.6 ± 5.7	32.2 ±5.5
Smoking – N (%)	110 (31.0%)	126 (14.6%)
Alcohol- N (%)	21 (5.9%)	42 (4.8%)
Drug use - N (%)	8 (2.2%)	9 (1.0%)
Years in full-time education[a]	12.8 ± 2.8	13.8 ± 3.1
Ethnic group		
- White	254 (71.3%)	641 (73.8%)
- Black	62 (17.4%)	118 (13.6%)
- Asian	27 (7.6%)	77 (8.9%)
- Mixed	8 (2.2%)	20 (2.3%)
- Other	5 (1.4%)	12 (1.4%)
Height - cm	163.6 ± 6.6	163.5 ± 6.6
Weight - kg	70.3 ± 15.7	72.2 ± 17.6
BMI (kg/m^2)	26.3 ± 5.5	27.0 ± 6.5
Systolic Blood Pressure - mmHg [b]	111.1 ± 12.0	112.2 ± 12.5
Diastolic Blood Pressure - mmHg [b]	65.4 ± 8.8	66.2 ± 8.5
Obstetric history		
Any previous pregnancy - N (%)	345 (97.2%)	827 (95.2%)

previous pregnancy of at least 14 weeks - N (%)	337 (94.9%)	812 (93.3%)
History of preterm birth (any) - N (%)	285 (80.3%)	681 (78.5%)
spontaneous preterm birth - N (%)[d]	265 (76.6%)	656 (76.5%)
History of live birth followed by neonatal death - N (%)	44 (12.4%)	121 (13.9%)
History of stillbirth -N (%)	29 (8.2%)	66 (7.6%)
Cervical length – mm[c]	28.4 ± 10.6	28.6 ± 11.0
Cervical length ≤25mm[c] - N (%)	77 (35.6%)	179 (36.1%)
Cervical length ≤15mm [c] - N (%)	25 (11.6%)	73 (14.7%)
Fibronectin testing in screening phase		
Gestation (weeks) at fFN test	22.9 (0.6)	22.9 (0.6)
Positive fFN test result - N (%)	103 (28.9%)	241 (27.7%)

Continuous variables are summarised as mean ± standard deviation (plus-minus values), categorical variables as number (percentage) per category. All variables are missing for a maximum of 5 women in each group, except where specified otherwise.

[a] Missing for 24 / 29 women in childhood outcome unavailable / available respectively.

[b] Missing for 1 / 6 women in childhood outcome unavailable / available respectively

[c] Missing for 141 / 373 women in childhood outcome unavailable / available respectively

[d] Missing for 11 / 12 women in childhood outcome unavailable / available respectively

Supplementary Table 2. Per protocol analyses of primary outcome

Outcome	OR	95% CI	P value	Adjusted P value*
Obstetric – death or preterm birth < 34 weeks n (%)	0.86	0.55, 1.35	0.51	1.00
Neonatal - composite of death, brain injury or severe CLD) n (%)	0.55	0.30, 0.99	0.046	0.14
	Treatment Effect	95% CI	P value	
Childhood – mean between-group difference in Bayley III at 2 years - cognitive composite score including imputations for deaths,	0.49	-2.22, 3.20	0.73	0.73

* Adjusted p-values are given to facilitate comparison with results in the ITT population.

Supplementary Table 3. Analysis performed with multiple imputations of primary outcome

Outcome	Parameter estimate or Hazard Ratio	95% confidence interval	p-value
Obstetric[a] outcome	0.866	0.640, 1.170	0.35
Neonatal[a] outcome	0.637	0.418, 0.971	0.036
Childhood outcome[b]	-0.019	-0.372, 0.334	0.91
Childhood outcome[c]	-0.051	-0.371, 0.269	0.74

Ten imputations were run.

[a] Variables used for predicting outcome: Previous pregnancy of at least 14 weeks, high/low risk, maternal age, sex.

[b] Variables used for predicting outcome: Gestational age, birth weight, Chronic Lung Disease, brain injury, previous pregnancy of at least 14 weeks, high/low risk, maternal age, sex.

[c] Variables used for predicting outcome: Birth weight, Chronic Lung Disease, brain injury, previous pregnancy of at least 14 weeks, high/low risk, maternal age, sex.

Note, for comparison with primary analysis: Adjusted p-values are: obstetric outcome p= 0.11, neonatal outcome p= 0.7, childhood outcome remains unchanged.

Supplementary Table 4

Characteristics of those participants who were and who were not included in the per protocol analysis.

Characteristic	**Not included in per protocol analysis (N=539)**	**Included in per protocol analysis (N=687)**
General		
Age - years	30.5 ± 5.7	32.2 ± 5.5
Smoking – N (%)	137 (25.7%)	99 (14.4%)
Alcohol- N (%)	32 (6.0%)	31 (4.5%)
Drug use - N (%)	7 (1.3%)	10 (1.5%)
Years in full-time education[a]	13.3 ± 3.1	13.6 ± 3.0
Ethnic group		
- White	374 (69.6%)	521 (75.8%)
- Black	97 (18.1%)	83 (12.1%)
- Asian	46 (8.6%)	58 (8.4%)
- Mixed	13 (2.4%)	15 (2.2%)
- Other	7 (1.3%)	10 (1.5%)
Height - cm	163.8 ± 6.8	163.3 ± 6.4
Weight - kg	71.7 ± 16.8	71.6 ± 17.3
BMI (kg/m^2)	26.7 ± 6.1	26.8 ± 6.4
Systolic Blood Pressure - mmHg	111.6 ± 12.4	112.0 ± 12.4
Diastolic Blood Pressure - mmHg	65.9 ± 9.0	66.0 ± 8.2
Obstetric history		

Any previous pregnancy - N (%)	525 (97.8%)	647 (94.2%)
previous pregnancy of at least 14 weeks - N (%)	515 (95.9%)	634 (92.3%)
History of preterm birth (any) - no (%)	429 (80.0%)	537 (78.2%)
spontaneous preterm birth - N (%)[c]	404 (77.0%)	517 (76.3%)
History of live birth followed by neonatal death - N (%)	73 (13.6%)	92 (13.4%)
History of stillbirth -N (%)	55 (10.2%)	40 (5.8%)
Cervical length – mm[b]	28.9 ± 10.7	28.2 ± 11.0
Cervical length ≤25mm[b] - N (%)	114 (34.7%)	142 (37.1%)
Cervical length ≤15mm [b] - N (%)	43 (13.1%)	55 (14.4%)
Fibronectin testing in screening phase		
Gestation (weeks) at fFN test	22.9 (0.7)	22.9 (0.6)
Positive fFN test result – N (%)	152 (28.2%)	192 (27.9%)

Continuous variables are summarised as mean ± standard deviation (plus-minus values), categorical variables as number (percentage) per category. All variables are missing for a maximum of 5 women in each group, except where specified otherwise.

[a] Missing for 59 / 44 women in excluded and included in per protocol analysis respectively.

[b] Missing for 210/304 women in excluded and included in per protocol analysis respectively

[c] Missing for 14/9 women in excluded and included in per protocol analysis respectively

Supplementary Table 5 Rates of preterm birth in subgroups

Supplementary table Primary obstetric outcome in subgroups.		
Risk group	Placebo	Progesterone
	Number with event / number with data available (percentage).	
Fibronectin status		
Fibronectin negative	54 / 418 (12.9)	51 / 442 (11.5)
Fibronectin positive	54 / 179 (30.2)	45 / 159 (28.3)
Cervical length at baseline		
> 25mm	29 / 228 (12.7)	25 / 217 (11.5)
≤ 25mm	38 / 118 (32.2)	33 / 133 (24.8)
Cervical length at baseline		
> 15mm	46 / 299 (15.4)	37 / 300 (12.3)
≤ 15mm	21 / 47 (44.7)	21 / 50 (42.0)
History of spontaneous preterm birth		
No	23 / 149 (15.4)	19 / 124 (15.3)
Yes	82 / 437 (18.8)	74 / 466 (15.9)
History of any preterm birth		
No	20 / 135 (14.8)	18 / 115 (15.7)
Yes	88 / 461 (19.1)	78 / 485 (16.1)

Supplementary text 1: TSC and DMC membership

The OPPTIMUM investigators are very grateful to the following for their participation in the Trial Steering and Data Monitoring Committees.

Trial Steering Committee:

John Morrison (Chair) National University of Ireland, Galway, Ireland; Denis Azzopardi, Imperial College, London, UK; Jane Brewin, Tommy's, the Baby Charity, London, UK; John M Davison, The Medical School, University of Newcastle, Newcastle, UK; Sara Kenyon, University of Birmingham, Birmingham, UK; Gillian Pillans, Lay representative, England, UK. Maggie Redshaw, NPEU, Oxford, UK.

Data Monitoring Committee: Henry Halliday (Chair) Royal Maternity Hospital, Belfast, Northern Ireland, UK; Simon Gates University of Warwick, Coventry, UK; Gerard H.A. Visser, University Medical Centre, Utrecht, Netherlands

Supplementary Text 2

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