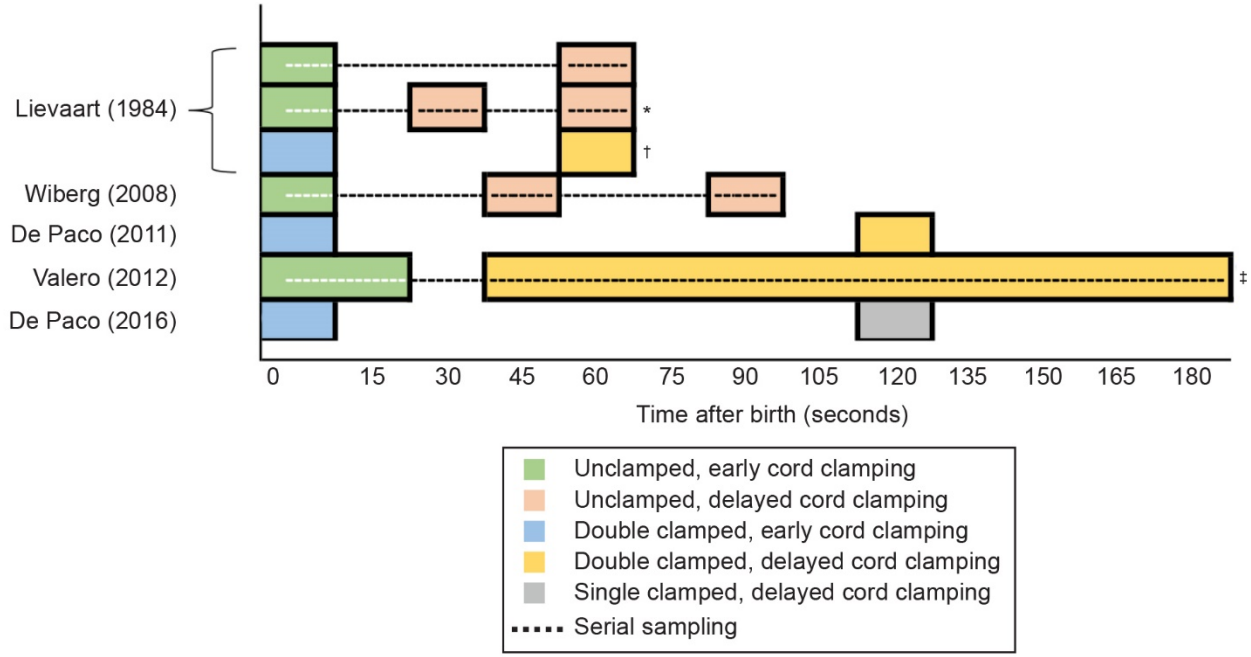
Appendix 1. Diagram of the varying delayed cord clamping durations and cord blood sampling methodologies from previous studies used to evaluate the effect of delayed cord clamping on umbilical blood gas in healthy term neonates. The bars represent when blood gas samples were procured. *We did not describe the results from this study arm due to the results being only partially described in the study. †We did not report the results of this study arm because they used nonpaired cord blood sampling. ‡Cord clamping occurred at >120 seconds in 38.1% of the neonates and at 180 seconds in 6.8% of neonates.



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Appendix 2. Risk of Bias Within Studies

Randomization – Low risk of bias. Both RCTs conducted by De Paco et al utilized adequate randomization.[1,2]

Treatment concealment and blinding – Low risk of bias. Treatment concealment and blinding of the patient and healthcare team were not performed in either RCT. However, the lack of treatment concealment or blinding may be of minimal concern given the limited opportunity for patient or staff to influence blood gas parameters in the brief amount of time between delivery, sample procurement, and blood gas analysis.

Deviations from intended treatment – Low risk of bias. Deviations from intended treatments were not reported in any of the studies. Although conversion from intended delayed cord clamping to early cord clamping (i.e. typically due to the need for resuscitation after birth) was not reported, it is less likely to have occurred since each study only included healthy singleton pregnancies that delivered at term.

Blood draw success (sample attrition) – Low risk of bias. Prior studies have reported greater difficulty procuring adequate volumes of venous and arterial umbilical blood with prolonged delayed cord clamping duration.[1-4] None of the five studies included in this reported on number of unsuccessful sampling. Successful sampling is likely dependent on clinician cord sampling skill and not a reflection of the placental/infant health and blood gas results. Hence, we would not expect the cord blood gas values of the potentially missing samples to be different from the samples included in these studies.

Arterial sample validation – Low risk of bias. The umbilical artery and vein are in close proximity to one another and inadvertent sampling and mixing from the opposite vessel has been shown to commonly occur in 19.5% of blood draws.[5] There is no consensus about a validation criteria. It has been suggested to validate

correct blood sampling by comparing pH and P_aCO_2 differences between paired arterial and venous cord blood gas samples.[6,7] Anderson et al used similar validation methods and showed similar rates of valid samples between delayed cord clamping and early cord clamping. Each included study procured paired venous and arterial cord samples, but validation of the blood samples was not reported. Although the potential inclusion of invalid samples would reduce the precision of the value ranges describing the cord blood parameters, it is unlikely the summary effect estimate (i.e. difference in means) describing the effect of delayed cord clamping would be biased.

Risk of Bias Across Studies

Publication bias. We were unable to perform our originally intended publication analysis (i.e. funnel plot) due to the lack of consistent summary estimates between the limited number of included studies. Based on the study sample sizes and the heterogeneity of outcomes we estimate that there was minimal risk of publication bias.

Indirectness.

Population. Each study used vaginally born healthy singleton term infants.

Early cord clamping duration. Accurate timing of when early cord clamping occurred was not described in any of the studies and some studies used different descriptions of when early cord clamping occurred (ex: 0 s, < 10 s, < 30 s). Early cord clamping in each study was at least < 30 s; however, the possible heterogeneity between the studies warranted a downgrade.

delayed cord clamping duration. The included studies collected cord blood gas samples at different delayed cord clamping duration times ranging between 45 s and 180 s which likely had an impact on the summary estimate across the studies. Both RCTs[1,2] evaluated the effects of delayed cord clamping at 120 s and found no difference in cord blood gas (except for arterial P_aO_2 in the 2011 De Paco et al study).[1] cord blood gas samples from the observational studies, however, were collected mostly at shorter durations and did observe a difference between early cord clamping and delayed cord clamping blood gas. This

heterogeneity warranted a downgrade.

Infant position during delayed cord clamping . Infant position during delayed cord clamping varied between the studies; some were held at the level of introitus while others were placed on the mother's abdomen. Although the two positions result in comparable increase in hematocrit,[8] whether infant position may affect cord blood gas parameters after delayed cord clamping has not been investigated.

Timing of the post-clamp blood draw and analysis. Each of these studies reported that samples were analyzed within 30 minutes of obtaining blood gases. Prior studies have demonstrated that pH, PCO_2, and PO_2 of arterial and venous blood stored in a doubly clamped segment of cord at room temperature can be measured reliably for up to 60 minutes after birth.[9] Therefore, it is unlikely that small differences in timing biased their findings. However, measurements of lactate concentration in arterial and venous cord blood become unreliable within 20 minutes of delivery whether sampled from clamped or unclamped vessels.[10]

Clamping method and serial samples. The three observational studies used an unclamped cord sampling method that allowed them to collect within-subject serial samples corresponding to early cord clamping and delayed cord clamping times.[3,11,12] Hence, infants acted as their own controls and summary estimate differences between early cord clamping and delayed cord clamping blood gas findings were not influenced by inter-subject variability. However, both RCTs by De Paco et al[1,2] however, obtained a single sample from each placenta either in the early cord clamping or delayed cord clamping group. Thus, their summary estimates may have been biased towards the null due to the influence of inter-subject variability related the use of separate infants to procure early cord clamping and delayed cord clamping blood gas samples.

Inconsistency. Despite the unavailability of common summary estimates with 95% CIs, the available gross estimates consistently suggest delayed cord clamping is associated with lower pH, HCO_3, and higher P_aCO_2, lactate and base deficit. Unlike the observational studies, the RCTs did not reach statistical significance although the

directionality of the gross estimates were similar. P_aO_2 was inconsistent across the studies although authors attributed this to methodological differences related to the timing of effective newborn respiration.[2,3,13-15] Overall the findings were fairly consistent.

Imprecision. Wiberg et al[3] and Lievaart et al[11] did not provide sufficient information to confidently evaluate the precision and clinical significance of their estimates. However, the directionality of their estimates coupled with the 95% CIs provided by Valero et al[12] and De Paco et al[1,2] provided sufficient precision to assess for clinical relevance.

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Appendix 3. Quality of Evidence Assessment Across the Studies

Quality of evidence	Judgment
Publication bias	-
Indirectness	Downgrade
Inconsistency	-
Imprecision	-
Risk of bias	-
Starting quality assessment	High quality
Final quality assessment	Moderate quality

Appendix 4. Summary of Study Results that Compared Umbilical Artery Blood Gas Parameters After Performing Early- vs. Delayed Cord Clamping

					Early cord clamping		Delayed cord clar	
Parameter	**Author**	**Study arm**	**Distribution metric**	**Units**	**n**	**Measure**	**n**	**Measure**
pH	De Paco[1]	< 10 s vs 120 s	*M (SD)* [95%CI][A]		55	7.24 (0.08) [7.22, 7.26]	44	7.24 (0.06) [7.22, 7.26]
	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]		50	7.28 (0.07) [7.26, 7.30]	45	7.26 (0.09) [7.23, 7.29]
	Valero[12]	< 30 vs pulse end	*M* (range) [95%CI]		60	7.30 (7.08 to 7.45)	60	7.27 (7.02 to 7.43)
	Wiberg[3]	0 vs 45 s	*M* (median)		55	7.24 (7.24)	60	7.22 (7.21)
		0 vs 90 s	*M* (median)				50	7.21 (7.22)
	Lievaart[11]	Unclamped 0 vs 60 s	*M* (median) (range)		14		14	
P_aO_2	De Paco[1]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmHg	55	17.0 (4.0) [15.9, 18.1]	44	23.0 (4.1) [21.8, 24.2]
	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmHg	50	25.0 (14.0) [21.1, 28.9]	45	22.5 (7.7) [20.2, 24.7]
	Valero[12]	< 30 vs pulse end	*M* (range) [95%CI]	mmHg	60	24.8 (5.1 to 50.7)	60	24.1 (7.3 to 49.3)
	Wiberg[3]	0 vs 45 s	*M* (median)	mmHg[D]	49	17.2 (17.3)[E]	49	19.6 (19.9)
		0 vs 90 s	*M* (median)	mmHg[D]	49		49	20.6 (20.4)[E]
P_aCO_2	De Paco[1]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmHg	55	46.2 (11.3) [43.2, 49.2]	44	49.3 (10.3) [46.2, 52.3]
	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmHg	50	50.0 (10.1) [47.2, 52.8]	45	51.7 (12) [48.2, 55.2]
	Valero[12]	< 30 vs pulse end	*M* (range) [95%CI]	mmHg	60	47.0 (29.8 to 81.1)	60	50.2 (30.2 to 82.0)
	Wiberg[3]	0 vs 45 s	*M* (median)	mmHg[D]	54	57.3 (55.7)	54	60.1 (58.3)
		0 vs 90 s	*M* (median)	mmHg[D]			54	60.5 (58.9)
	Lievaart[11]	Unclamped 0 vs 60 s	*M* (median) (range)	mmHg	14		14	
HCO_3	De Paco[1]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmol/L	55	20.5 (3.1) [19.7, 21.3]	44	21.3 (3.2) [20.4, 22.3]
	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmol/L	50	22.5 (2.5) [21.8, 23.2]	45	22.1 (2.6) [21.3, 22.9]
	Valero[12]	< 30 vs pulse end	*M* (range) [95%CI]	mmol/L	60	21.0 (14.7 to 27.3)	60	20.8 (12.0 to 26.7)
	Wiberg[3]	0 vs 45 s	*M* (median)	mmol/L	54	18.9 (18.6)[E]	54	18.4 (18.2)
		0 vs 90 s	*M* (median)	mmol/L			54	18.1 (17.9)
Lactate	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmol/L	50	3.8 (1.5) [3.4, 4.2]	45	4.1 (1.6) [3.6, 4.6]

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	Valero[12]	< 30 vs pulse end	*M* (range) [95%CI]	mmol/L[C]	60	1.7 (0.7 to 3.2)	60	1.9 (0.7 to 4.9)
	Wiberg[3]	0 vs 45 s	*M* (median)	mmol/L	50	5.3 (4.8)[E]	50	5.7 (5.3)[E]
		0 vs 90 s	*M* (median)	mmol/L			50	5.9 (5.4)[E]
Base Deficit	Valero[12]	< 30 vs pulse end	*M* (range) [95%CI]	mmol/L	60	4.0 (1.5 to 11.9)	60	4.4 (0.4 to 9.6)
	Wiberg[3]	0 vs 45 s	*M* (median)	mmol/L[F]	54	4.8 (4.8)[E]	54	5.6 (5.8)
		0 vs 90 s	*M* (median)	mmol/L[F]			54	6.1 (6.5)[E]
	Lievaart[11]	Unclamped 0 vs 60 s	*M* (median) (range)	mmol/L	14		14	

All cord blood gas values were rounded to one decimal place except pH

[A] 95%CI for mean and for difference in means were calculated using the following equations: $M \pm 1.96\ (SD/\sqrt{n})$ and $M_1 - M_2 \pm 1.96 \sqrt{(SD_1^2/n_1 + SD_2^2/n_2)}$

[B] *P* values were based on the following: Valero and Wiberg = Wilcoxon signed-rank; De Paco 2011 = Students t test; De Paco 2016 = Mann-Whitney test; Lievaart = Sign test

[C] Units were converted from mg/dL to mmol/L

[D] Units were converted from kPa to mmHg

[E] Author noted these are skewed distributions

[F] Units were converted from base excess to base deficit

[G] Slightly overestimated because they excluded 1 infant with a decrease in P_aCO_2 between 0 to 60 s.

[H] Difference in means was not provided in the study so we calculated it using the following equation: $M_1 - M_2$

ns = not significant

* = *p* value <.05

** = *p* value <.01

*** = *p* value <.001

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Appendix 5. Summary of Study Results that Compared Umbilical Venous Blood Gas Parameters After Performing Early- vs. Delayed Cord Clamping

					Early cord clamping		Delayed cord clamping	
Parameter	**Author**	**Study arm**	**Distribution metric**	**Units**	**n**	**Measure**	**n**	**Measure**
pH	De Paco[1]	< 10 s vs 120 s	*M (SD)* [95%CI][A]		65	7.32 (0.05) [7.31, 7.33]	51	7.31 (0.05) [7.30, 7.32]
	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]		50	7.35 (0.06) [7.33, 7.37]	45	7.33 (0.08) [7.31, 7.35]
	Wiberg[3]	0 vs 45 s	*M* (median)		62	7.32 (7.33)[E]	60	7.31 (7.33)
		0 vs 90 s	*M* (median)				60	7.31 (7.32)[E]
	Lievaart[11]	Unclamped 0 vs 60 s	Range		12		12	
P_vO_2	De Paco[1]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmHg	65	25.9 (5.5) [24.5, 27.2]	51	24.8 (5.5) [23.3, 26.3]
	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmHg	50	27.6 (6.1) [25.9, 29.3]	45	27.8 (8.0) [25.5, 30.1]
	Wiberg[3]	0 vs 45 s	*M* (median)	mmHg[D]	59	27.8 (26.8)	59	28.3 (27.6)
		0 vs 90 s	*M* (median)	mmHg[D]			59	27.6 (26.8)
P_vCO_2	De Paco[1]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmHg	65	38.4 (4.6) [37.3, 39.5]	51	38.94 (5.9) [37.3, 40.5]
	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmHg	50	40.6 (7.1) [38.6, 42.6]	45	42.0 (10.7) [38.9, 45.1]
	Wiberg[3]	0 vs 45 s	*M* (median)	mmHg[D]	62	42.7 (40.7)[E]	62	42.8 (40.3)[E]
		0 vs 90 s	*M* (median)	mmHg[D]			62	43.6 (40.7)[E]
	Lievaart[11]	Unclamped 0 vs 60 s	Range	mmHg	12		12	
HCO_3	De Paco[1]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmol/L	65	20.9 (2.8) [20.2, 21.6]	51	20.6 (3.0) [19.7, 21.4]
	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmol/L	50	21.4 (1.7) [20.9, 21.9]	45	21.1 (2.1) [20.5, 21.7]
	Wiberg[3]	0 vs 45 s	*M* (median)	mmol/L	62	19.5 (19.6)	62	19.5 (19.4)
		0 vs 90 s	*M* (median)	mmol/L			62	19.3 (19.1)
Lactate	De Paco[2]	< 10 s vs 120 s	*M (SD)* [95%CI][A]	mmol/L	50	3.3 (1.2) [3.0, 3.6]	45	3.5 (1.5) [3.1, 3.9]
	Wiberg[3]	0 vs 45 s	*M* (median)	mmol/L	56	5.0 (4.7)[E]	56	5.1 (4.7)[E]
		0 vs 90 s	*M* (median)	mmol/L			56	5.3 (5.0)[E]
Base Deficit	Wiberg[3]	0 vs 45 s	*M* (median)	mmol/L[F]	61	4.9 (5.1)	61	5.0 (5.4)
		0 vs 90 s	*M* (median)	mmol/L[F]			61	5.2 (5.6)[E]

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Lievaart[11]	Unclamped 0 vs 60 s	Range	mmol/L	12		12

All cord blood gas values were rounded to one decimal place except pH

[A] 95%CI for mean and for difference in means were calculated using the following equations: $M \pm 1.96 (SD/\sqrt{n})$ and $M_1 - M_2 \pm 1.96 \sqrt{(SD_1^2/n_1 + SD_2^2/n_2)}$

[B] *P* values were based on the following: Valero and Wiberg = Wilcoxon signed-rank; De Paco 2011 = Students t test; De Paco 2016 = Mann-Whitney test; Lievaart = Sign test

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