Supplementary Material

Sex differences in patent ductus arteriosus incidence and response to pharmacological treatment in preterm infants: A systematic review, meta-analysis and meta-regression

Table S1. Search strategy

Pubmed ((Sex[MESH] OR Sex Characteristics[MESH] OR Sex Distribution[MESH] OR "Sex Characteristic*"[tiab] OR "Gender Difference*"[tiab] OR "Sex Dimorphism*"[tiab] OR "Gender Characteristic*"[tiab] OR "Sex Difference*"[tiab] OR "Sex Distribution*"[tiab] OR "Gender Distribution*"[tiab] OR "Male Disadvantage"[tiab] OR "Female Advantage"[tiab] OR risk [tiab]) AND (Patent ductus arteriosus[MESH] OR "Patency of the Ductus Arteriosus"[tiab] OR "Ductus Arteriosus"[tiab] OR "Ductus Botalli"[tiab] OR "PDA"[tiab]))
Embase ((exp Sex Characteristics/ OR exp Sex Distribution / OR exp Sex Factors/) OR ("male disadvantage" or "female advantage" or gender or sex or "gender difference" or "gender differences" or "sex difference" or "sex differences" or "gender differential" or "gender differentials" or "sex differential" or "sex differentials" or "sexual dimorphism" or "sexually dimorphic")) AND (patent ductus arteriosus))

Table S2. Characteristics of the included studies

First author, year	Country	Prospective?	Total infants	Centers	Mean/median GA cohort	Mean/median BW cohort	Independent variable	Outcomes	PDA primary outcome	Selection	Comparability	Outcome/ Exposure	Total NOS
Adrouche-Amrani2012 (1)	USA	No	79	1	25.8	770.7	PDA	hsPDA / Treatment	YES	3	1	3	**7**
Ahamed 2015 (2)	USA	No	203	1	26.5	840.6	PDA	hsPDA / Treatment	NO	3	1	3	**7**
Ahmed 2020 (3)	Egypt	Yes	75	1	31.7	ND	PDA	Any PDA	YES	2	1	3	**6**
Aikio 2014 (4)	Finland	No	88	1	28.6	1308.0	PDA	hsPDA	YES	3	1	3	**7**
Akar 2019 (5)	Turkey	No	389	1	29.5	1054.8	PDA	hsPDA	YES	3	2	2	**7**
Alan 2013 (6)	Turkey	Yes	25	1	27.8	988.1	PDA	hsPDA	YES	3	1	3	**7**
Antonucci 2009 (7)	Italy	Yes	40	1	29.5	1305.0	PDA	hsPDA	NO	2	2	3	**7**
Asrani 2018 (8)	USA	Yes	70	1	27.9	1014.3	PDA	hsPDA	YES	3	2	3	**8**
Bas 2014 (9)	Spain	No	194	2	27.9	1008.5	PDA	hsPDA / Treatment	YES	3	1	3	**7**
Becerra 2013 (10)	Mexico	Yes	66	1	28.0	950.0	PDA	hsPDA	YES	3	1	3	**7**
Bekmez 2018 (11)	Turkey	No	212	1	29.0	1237.8	PDA	hsPDA	YES	3	2	3	**8**
Bertino 2009 (12)	Italy	Yes	262	1	30.4	1140.0	Sex	hsPDA	NO	3	2	2	**7**
Boghossian 2018 (13)	USA	No	194112	852	26.0	919	Sex	hsPDA	NO	4	2	3	**9**
Bonamy 2017 (14)	11 European countries	No	6896	Multi	29.1	1223.0	PDA	hsPDA	NO	4	1	3	**8**
Boo 2006 (15)	Malaysia	Yes	60	1	28.3	1115.8	PDA	Treatment	NO	3	2	3	**8**
Bravo 2011 (16)	Spain	Yes	90	1	28.4	1066.7	PDA	Treatment	YES	4	2	3	**9**
Breatnach 2017a (17)	Ireland	No	121	1	26.8	968.0	PDA	Any PDA	NO	3	2	3	**8**
Breatnach 2017b (18)	Ireland	No	51	1	27	1060	PDA	Any PDA	NO	3	1	3	**7**
Brooks 2005 (19)	Australia	No	252	1	26.0	900.5	PDA	Treatment	YES	3	2	3	**8**
Brunner 2013 (20)	Austria	Yes	322	1	28.5	1174.0	PDA	Any PDA	NO	3	1	3	**7**

First author, year	Country	Prospective?	Total infants	Centers	Mean/median GA cohort	Mean/median BW cohort	Independent variable	Outcomes	PDA primary outcome	Selection	Comparability	Outcome/ Exposure	Total NOS
Buddhe 2012 (21)	USA	Yes	69	2	27.6	981.0	PDA	hsPDA	YES	3	1	3	**7**
Cakir 2019 (22)	Turkey	No	799	1	28.0	1068.2	PDA	hsPDA	YES	4	2	3	**9**
Chen 2015 (23)	China	Yes	77	1	29.5	1152.7	PDA	Any PDA / Treatment	NO	3	1	3	**7**
Chessex 2010 (24)	Canada	Yes	40	1	25.4	752.0	Sex	hsPDA	NO	2	2	3	**7**
Chock 2011 (25)	USA	Yes	31	2	26.2	850.9	PDA	hsPDA / Any PDA /Treatment	NO	2	2	3	**7**
Chock 2014 (26)	USA	No	187	1	27.6	1004.9	PDA	hsPDA	NO	3	1	3	**7**
Chock 2016 (27)	USA	Yes	47	1	27.2	865.4	PDA	hsPDA / Any PDA	NO	3	2	3	**8**
Choi 2005 (28)	Korea	Yes	66	1	29.9	1356.0	PDA	hsPDA	YES	3	2	3	**8**
Clyman 2020 (29)	North America	No	407	1	26.2	831.3	PDA	hsPDA	NO	3	1	3	**7**
Collins 2018 (30)	USA	Yes	1090	8	33.0	1410.8	PDA	hsPDA / Any PDA	NO	4	1	3	**8**
Coviello 2020 (31)	Italy	Yes	60	1	28.8	1223.2	PDA	hsPDA	YES	3	2	3	**8**
Dagle 2009 (32)	USA	No	366	1	27.9	1042.9	PDA	Any PDA	NO	3	2	3	**8**
Dagle 2019 (33)	USA	No	1013	Multi	25.9	762.7	PDA	hsPDA	YES	4	1	3	**8**
Dani 2008 (34)	Italy	Yes	34	1	25.6	786.7	PDA	hsPDA /Any PDA /Treatment	YES	4	2	3	**9**
Demir 2016 (35)	Turkey	No	235	1	29.0	1548.5	PDA	hsPDA	YES	4	1	3	**8**
Derzbach 2005 (36)	Hungary	No	140	1	29.0	1189.8	Sex	hsPDA	NO	3	2	3	**8**
Dix 2016 (37)	The Netherlands	Yes	398	1	29.1	1312.4	PDA	hsPDA /Any PDA /Treatment	YES	3	1	3	**7**
El-Khuffash 2008 (38)	Ireland	Yes	80	1	28.0	1060.0	PDA	hsPDA /Any PDA	NO	3	2	3	**8**
Elsmen 2004 (39)	Sweden	No	175	1	26.0	771.0	Sex	hsPDA	NO	3	1	3	**7**
Engeseth 2020 (40)	Germany	Yes	228	1	26.7	865.4	PDA	Any PDA / Treatment	NO	3	1	3	**7**
Engür 2015 (41)	Turkey	No	63	1	29.8	1330.8	PDA	hsPDA/ Any PDA	YES	3	2	3	**8**

First author, year	Country	Prospective?	Total infants	Centers	Mean/median GA cohort	Mean/median BW cohort	Independent variable	Outcomes	PDA primary outcome	Selection	Comparability	Outcome/ Exposure	Total NOS
Fink 2018 (42)	Israel	No	72	1	27.3	1016.4	PDA	hsPDA	YES	3	2	3	**8**
Flood 2015 (43)	USA	No	221	1	ND	1680.0	PDA	Any PDA	YES	3	2	3	**8**
Furzan 1985 (44)	USA	Yes	120	1	29.4	1165.0	PDA	hsPDA	YES	4	2	3	**9**
Ghirardello 2020 (45)	Italy	Yes	151	1	29.1	1098.4	PDA	hsPDA	YES	3	1	3	**7**
Godambe 2006 (46)	Canada	No	107	1	26.3	887.4	PDA	Treatment	YES	3	2	3	**8**
Gomez-Pomar 2017 (47)	USA	Yes	31	1	26.0	846.7	PDA	Any PDA	NO	2	2	3	**7**
Goudjil 2013 (48)	France	Yes	44	1	28.5	1209.5	PDA	hsPDA	NO	3	1	3	**7**
Griesmaier 2014 (49)	Austria	No	156	1	30.5	1393.9	PDA	Any PDA	NO	3	1	3	**7**
Grosfeld 1996 (50)	USA	Yes	1016	1	28.4	1053.8	PDA	hsPDA/ Treatment	NO	4	1	3	**8**
Halil 2018 (51)	Turkey	No	162	1	27.7	986.2	PDA	Treatment	YES	3	1	3	**7**
Halliday 1979 (52)	USA	Yes	36	1	27.9	906.7	PDA	Treatment	Yes	3	1	3	**7**
Hammoud 2003 (53)	Kuwait	No	101	1	29.9	1094.4	PDA	hsPDA	YES	3	1	3	**7**
Härkin 2016 (54)	Finland	No	23	1	28.4	1150	PDA	Treatment	YES	3	1	3	**7**
Härkin 2018 (55)	Finland	No	3668	Multi	29.1	1243.0	PDA	hsPDA / Treatment	YES	4	1	3	**8**
Harris 2018 (56)	New Zealand	No	51	1	27.8	1093.8	PDA	hsPDA	NO	3	2	3	**8**
Harris 2020 (57)	UK	Yes	318	Multi	26.9	894.8	Sex	Any PDA	NO	3	1	4	**8**
Hintz 2006 (58)	USA	No	2553	1	25.3	767.1	Sex	Any PDA	NO	4	1	3	**8**
Hoodbhoy 2009 (59)	UK	Yes	44	1	25.7	763.9	PDA	Any PDA	NO	3	2	3	**8**
Hsu 2010 (60)	Taiwan	Yes	31	1	30.0	1396.0	PDA	Treatment	NO	2	2	3	**7**
Hsu 2019 (61)	Taiwan	No	18	1	27.6	1075.0	PDA	Treatment	YES	3	1	3	**7**
Inayat 2015 (62)	USA	Yes	53	1	26.6	971.9	PDA	hsPDA	YES	4	2	3	**9**
Isayama 2015 (63)	Japan,	No	6183	Multi	27.9	1052.2	PDA	hsPDA	NO	4	2	3	**9**

First author, year	Country	Prospective?	Total infants	Centers	Mean/median GA cohort	Mean/median BW cohort	Independent variable	Outcomes	PDA primary outcome	Selection	Comparability	Outcome/ Exposure	Total NOS
	Canada												
Ito 2017 (64)	Japan	No	38023	Multi	28.0	1034	Sex	hsPDA	NO	4	1	3	**8**
Janz-Robinson 2015 (65)	Australia	No	1473	10	26.5	945.0	PDA	hsPDA / Treatment	NO	4	1	3	**8**
Jennische 2003 (66)	Sweden	No	64	1	28.9	1306	Sex	hsPDA	NO	3	1	3	**7**
Jhaveri 2010 (67)	USA	No	396	1	25.8	828.6	PDA	Treatment	YES	3	1	3	**7**
Jim 2005 (68)	China	Yes	77	1	28.2	1087.2	PDA	hsPDA	NO	4	2	3	**9**
Jones 2005 (69)	Canada	Yes	3117	17	27.4	1071	Sex	hsPDA	NO	4	2	3	**9**
Juujärvi 2018 (70)	Finland	No	295	1	26.4	821.7	PDA	Treatment	YES	3	1	3	**7**
Kahvecioglu 2018 (71)	Turkey	Yes	60	1	27.8	1024.6	PDA	Any PDA	YES	3	1	3	**7**
Kara 2019 (72)	Turkey	Yes	60	1	29.0	1069.2	PDA	hsPDA	YES	3	1	3	**7**
Karabulut 2019 (73)	Turkey	No	148	2	28.8	1092.0	PDA	hsPDA	YES	3	2	3	**8**
Katheria 2018 (74)	USA	No	292	1	28.4	1202.1	PDA	hsPDA	YES	3	2	3	**8**
Kaur 2019 (75)	Canada	No	183	1	26.4	870.0	PDA	Treatment	YES	3	1	3	**7**
Kazanci 2019 (76)	Turkey	No	481	1	28.0	1067.7	PDA	hsPDA	YES	4	2	3	**9**
Kent 2012 (77)	Australia	No	2549	1	26.3	923.0	Sex	hsPDA	NO	4	1	3	**8**
Kim 2010 (78)	Korea	Yes	78	1	26.5	742.0	PDA	Treatment	YES	2	2	3	**7**
Kim 2012 (79)	Korea	Yes	28	1	32.7	1918.0	PDA	hsPDA	YES	2	2	3	**7**
Kwinta 2009 (80)	Poland	Yes	60	1	28.5	1087.0	PDA	hsPDA	YES	4	2	3	**9**
Laughon2007 (81)	USA	No	28413	220	28.2	1089.7	PDA	hsPDA	YES	3	2	3	**8**
Lauterbach 2001 (82)	USA	No	51	1	32.3	2009.9	Sex	hsPDA	NO	2	1	3	**6**
Ledo 2017 (83)	Spain	Yes	72	1	28.1	1154.6	PDA	hsPDA /Any PDA	NO	3	1	3	**7**
Leonhardt 1987 (84)	Germany	Yes	32	1	30.0	1095.0	PDA	Treatment	YES	3	2	3	**8**
Letshwiti 2014 (85)	Ireland	Yes	69	1	28.6	1119.0	PDA	hsPDA	YES	4	2	3	**9**

First author, year	Country	Prospective?	Total infants	Centers	Mean/median GA cohort	Mean/median BW cohort	Independent variable	Outcomes	PDA primary outcome	Selection	Comparability	Outcome/ Exposure	Total NOS
Li 2013 (86)	Multiple country	No	289	1	27.7	1089.0	PDA	hsPDA	NO	2	2	3	**7**
Louis 2018 (87)	Canada	No	98	1	25.4	772.0	PDA	Treatment	YES	3	1	3	**7**
Madan 2008 (88)	USA	No	210	1	26.3	914.7	PDA	Treatment	YES	3	2	3	**8**
Madan 2009 (89)	USA	Yes	2300	Multi	25.2	736.2	PDA	Treatment	NO	4	2	2	**8**
Martin 1982 (90)	USA	Yes	20	1	31.2	1629.5	PDA	hsPDA /Any PDA	NO	3	1	3	**7**
Meinarde 2016 (91)	Argentina	No	88	1	28.4	1112.0	PDA	hsPDA	YES	3	1	3	**7**
Mellander 1984 (92)	USA	Yes	42	1	27.8	830.0	PDA	Treatment	YES	3	2	3	**8**
Mine 2013 (93)	Japan	Yes	46	1	28.1	954.4	PDA	hsPDA	YES	4	2	3	**9**
Natarajan 2013 (94)	USA	No	968	Multi	25.8	761.5	PDA	hsPDA	NO	4	2	3	**9**
Nemerofsky 2008 (95)	USA	Yes	125	1	27.5	1019.0	PDA	hsPDA	YES	4	2	3	**9**
Neubauer 2012 (96)	Austria	Yes	408	1	29.3	1259.2	Sex	hsPDA	NO	4	1	3	**8**
Nizarali 2012 (97)	Portugal	No	318	1	29.0	1139.2	PDA	hsPDA	NO	3	2	3	**8**
Nuntnarumit 2009 (98)	Thailand	Yes	35	1	30.3	1322.3	PDA	hsPDA	YES	2	2	3	**7**
Oh 2020 (99)	Korea	No	92	1	27.0	939.9	PDA	Treatment	YES	3	2	3	**8**
Okur 2019 (100)	Turkey	Yes	119	1	28.6	1068.6	PDA	hsPDA	YES	3	1	3	**7**
Oliveira 2016 (101)	Portugal	No	328	1	30.0	1231.0	PDA	Any PDA	YES	4	1	3	**8**
Olsson 2018 (102)	Sweden	Yes	47	1	25.2	738.3	PDA	hsPDA	YES	3	1	3	**7**
Olsson 2019 (103)	Sweden	Yes	60	1	25.3	732.3	PDA	hsPDA	YES	3	1	3	**7**
Olukman 2017 (104)	Turkey	No	824	1	29.6	1193.1	PDA	hsPDA	YES	4	2	3	**9**
O´Rourke 2008 (105)	Ireland	No	95	1	28.8	1000.0	PDA	hsPDA	NO	3	1	3	**7**
Patole 2007 (106)	Australia	No	252	1	26.0	900.5	PDA	hsPDA /Any PDA	NO	4	2	3	**9**
Peacock 2012 (107)	United Kingdom	Yes	797	Multi	26.5	853.0	Sex	Any PDA	NO	4	1	2	**7**

First author, year	Country	Prospective?	Total infants	Centers	Mean/median GA cohort	Mean/median BW cohort	Independent variable	Outcomes	PDA primary outcome	Selection	Comparability	Outcome/ Exposure	Total NOS
Pees 2010 (108)	Germany	Yes	15	1	26.2	853.8	PDA	hsPDA / Treatment	YES	2	2	3	**7**
Pereira 2018 (109)	UK	No	59	1	25.8	817.0	PDA	hsPDA / Treatment	YES	3	2	3	**8**
Polat 2016 (110)	Turkey	Yes	58	1	26.6	824.1	PDA	hsPDA	YES	2	2	3	**7**
Pourarian 2017 (111)	Iran	Yes	200	1	32.1	1741.0	PDA	hsPDA /Any PDA	YES	3	1	3	**7**
Reller 1985 (112)	USA	Yes	50	1	29.2	1166.4	PDA	hsPDA	YES	3	1	3	**7**
Rodriguez 2018 (113)	Spain	Yes	85	1	29.8	1222.6	PDA	hsPDA	YES	4	2	3	**9**
Romagnoli 2018 (114)	USA	Yes	65	1	27.5	1019.0	BW	Any PDA	YES	2	1	3	**6**
Rooney 2019 (115)	USA	Yes	144	1	26.0	ND	PDA	Treatment	YES	2	2	3	**7**
Sadeck 2014 (116)	Brazil	No	494	16	27.3	787.1	PDA	hsPDA / Treatment	YES	3	1	3	**7**
Sallmon 2012 (117)	Germany	No	1350	2	28.3	1060.0	PDA	hsPDA /Any PDA /Treatment	YES	4	2	3	**9**
Sallmon 2018 (118)	Germany	No	471	2	26.0	867.0	PDA	Treatment	YES	3	2	3	**8**
Sanjeev 2005 (119)	USA	Yes	29	2	26.3	873.5	PDA	hsPDA	YES	3	2	2	**7**
Schwarz 2018 (120)	Germany	Yes	22	1	28.6	1076.0	PDA	hsPDA	YES	3	1	3	**7**
Sellmer 2013 (121)	Denmark	Yes	183	1	28.1	1066.1	PDA	hsPDA/ Any PDA	NO	3	1	3	**7**
Semberova 2017 (122)	Ireland	No	280	3	28.9	1126.3	PDA	Any PDA	YES	3	2	3	**8**
Seon 2013 (123)	Korea	No	58	1	27.1	946.0	PDA	Treatment	NO	3	1	2	**6**
Shah 2011 (124)	USA	Yes	497	1	25.8	825.1	PDA	Any PDA /Treatment	YES	3	2	3	**8**
Skiold 2014 (125)	Sweden	Yes	107	1	25.6	800.6	Sex	hsPDA	NO	3	1	3	**7**
Stark 2011 (126)	Australia	Yes	60	1	30.0	1287.5	BW	hsPDA	NO	3	1	3	**7**
Steiner 2015 (127)	Austria	No	34	1	26.0	807.0	Sex	Treatment	YES	2	2	3	**7**
Stevenson 2000 (128)	USA	No	6738	12	28,5	~1100	Sex	hsPDA	NO	4	1	3	**8**
Strauss 2011 (129)	Israel	No	120	1	27.9	1019.0	PDA	hsPDA	YES	3	2	3	**8**

First author, year	Country	Prospective?	Total infants	Centers	Mean/median GA cohort	Mean/median BW cohort	Independent variable	Outcomes	PDA primary outcome	Selection	Comparability	Outcome/ Exposure	Total NOS
Tauber 2016 (130)	USA	Yes	95	1	28.5	1185.2	PDA	hsPDA/ Any PDA	NO	3	2	3	**8**
Terek 2014 (131)	Turkey	No	292	1	29.7	1470.2	PDA	hsPDA/ Any PDA	YES	3	1	3	**7**
Tioseco 2006 (132)	USA	No	833	1	30.9	1546.8	Sex	hsPDA	NO	4	2	2	**8**
Uchiyama 2011 (133)	Japan	No	57	1	28.3	1040.6	PDA	Treatment	NO	2	2	3	**7**
Vaidya 2021 (134)	USA	No	66	1	25.5	783	BW	Treatment	YES	3	1	3	**7**
Van de Bor 1988 (135)	Netherlands	No	1252	Multi	30.5	1269.7	PDA	hsPDA	NO	4	2	3	**9**
Velazquez 2018 (136)	USA	No	151	1	26.0	800.3	PDA	hsPDA	NO	3	1	3	**7**
Vieux 2010 (137)	France	No	148	3	28.3	1114.3	PDA	hsPDA	NO	3	1	3	**7**
Visconti 2013 (138)	Brazil	No	67	1	28.2	1063.3	PDA	hsPDA	YES	4	2	3	**9**
Weiss 1995 (139)	USA	Yes	77	1	27.8	1076.6	PDA	Treatment	YES	3	1	3	**7**
Weisz 2017 (140)	Canada	No	754	3	25.8	812.3	PDA	Treatment	YES	4	1	3	**8**
Yang 2008 (141)	Singapore	No	139	1	26.3	807.3	PDA	Treatment	NO	3	1	3	**7**
Yoon 2007 (142)	Korea	No	29	3	31.4	1651.2	PDA	Treatment	YES	3	1	3	**7**
Yum 2018 (143)	Korea	Yes	71	1	27.9	1038.3	PDA	hsPDA	YES	3	2	3	**8**
Zanardo 2008 (144)	Italy	Yes	46	1	27.5	1031.3	PDA	Treatment	YES	3	1	3	**7**
Zisk 2011 (145)	USA	No	12807	Multi	29.4	1358.6	Sex	hsPDA/ Any PDA	NO	4	2	3	**9**
Zozaya 2019 (146)	Spain	No	ND	Multi	ND	ND	Sex	hsPDA	NO	4	1	3	**8**

hs: hemodynamically significant; NOS: Newcastle-Ottawa Scale; PDA: patent ductus arteriosus

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Table S3. Meta-regression of continuous covariates.

Meta-analysis	Covariate	K	*Coefficient*	95% CI		P	R^2 analog
				Lower limit	Upper limit		
Any PDA vs. closed DA	GA total cohort (weeks)	80	0.002	-0.012	0.020	0.871	0.00
	Median year of cohort	72	-0.002	-0.006	0.002	0.332	0.00
hsPDA vs.(small PDA + closed DA)	GA total cohort (weeks)	36	0.014	-0.020	0.049	0.408	0.00
	Median year of cohort	34	0.000	-0.010	0.010	0.998	0.00
hsPDA vs small PDA	GA total cohort (weeks)	28	-0.009	-0.062	0.043	0.723	0.00
	Median year of cohort	23	0.009	0.001	0.0160	0.884	0.00
Responders vs non responders	GA total cohort (weeks)	45	-0.016	-0.039	0.007	0.169	0.00
	Median year of cohort	41	0.003	-0.005	0.005	0.965	0.00

GA: gestational age; hs: hemodynamically significant; PDA: patent ductus arteriosus

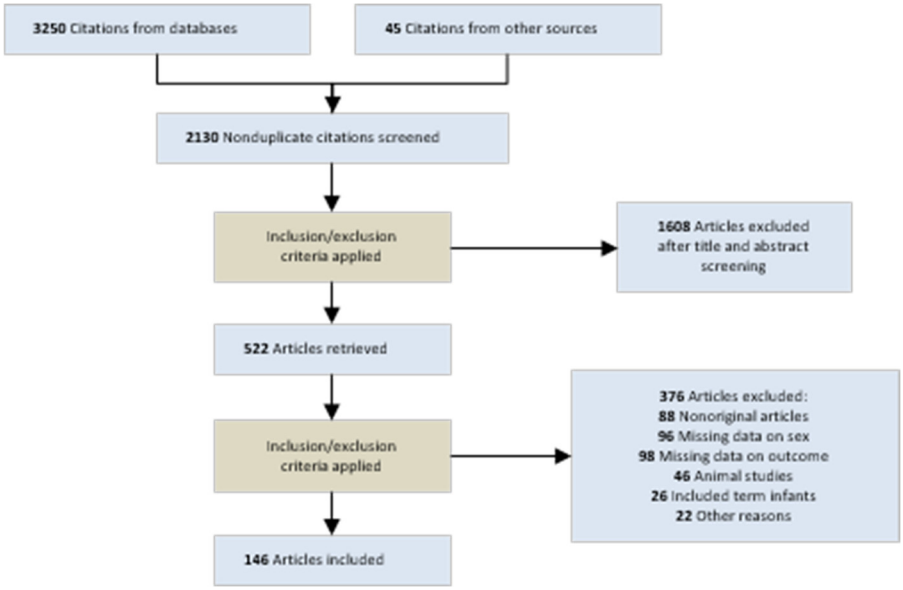

Figure S1. Flow diagram of the systematic search.

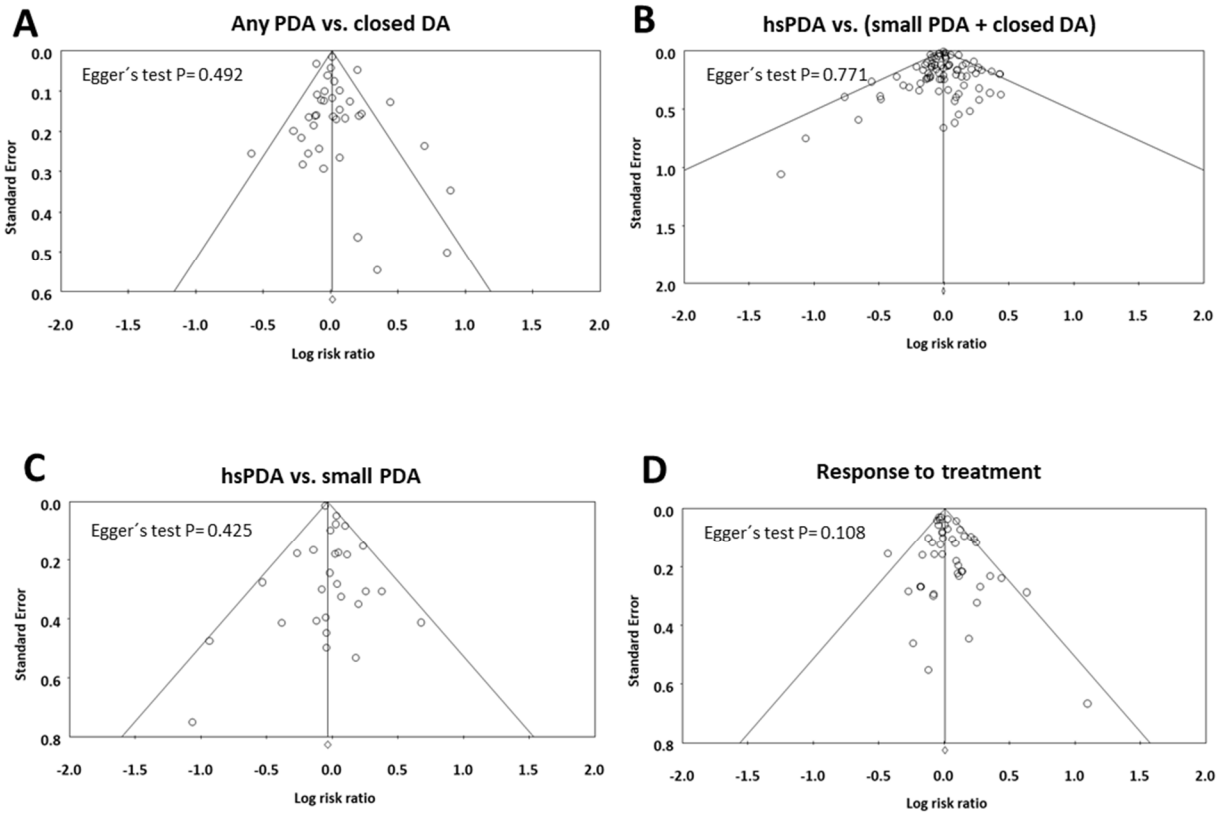

Figure S2. Funnel plot for publication bias analysis for the studies included in the different meta-analyses.

hs: hemodynamically significant. PDA: patent ductus arteriosus