REFLUX NEPHROPATHY AND THE RISK OF ADVERSE PREGNANCY RELATED OUTCOMES A systematic review and meta-analysis of case series and reports in the new millennium

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Introduction and objectives: Reflux nephropathy is a common urinary tract malformation, and a substantial cause of morbidity in women of childbearing age. While recent studies provide information on pregnancy-related outcomes, a systematic, meta-analytic review is not yet available and may help interpreting their heterogeneous results. The aim of the present study is to analyze pregnancy-related outcomes in literature on



reflux nephropathy, to perfect the estimation of the risks,
and to identify specific research needs.

Methods:

Medline, EMBASE and the Cochrane review databases were searched from January 2000 to May 31st 2016. Anticipating the retrieval of low number of series, and of heterogeneous designs and definitions, eligibility criteria were kept broad. Thus, we included all published studies that discussed reflux nephropathy in pregnancy and that reported on at least one pregnancy-related outcome. Data was extracted of eligible case series (≥6 cases). No study had a control group, not allowing for contextualization of results. For the outcomes preeclampsia (PE), pregnancy-induced hypertension (PIH), preterm birth, and newborns small for gestational age, we therefore employed as a control group the low-risk pregnancies from a multicenter Italian database (TOCOS) including 1418 live born singletons gathered in two Italian Centers (Torino and Cagliari). Case reports were analyzed narratively.

Results:

The search retrieved 2507 papers, of which 7 case series and 4 case reports were included. The series report on 434 women with 879 pregnancies, no study reported on controls. There is high heterogeneity for the study designs, number of pregnancies (26 to 242), setting of the study and study aim. Compared to the low-risk control cohort, the meta-analysis showed an **increased risk of PIH** (OR 5.55; CI 3.56- 8.66), **PE** (OR 6.04; CI 2.41-15.13), and a **ten-fold increased risk of all hypertensive disorders combined** (OR 10.43; CI 6.90-15.75). **No difference was observed in preterm delivery and caesarean sections**. A higher incidence of stillbirth was reported in one paper. The case reports warn against a severe complication, hydro(uretero)nephrosis with or without infection, reported in all 10 patients. In spite of the complications described in the mothers, all reported foetal outcomes were good, even if details are missing in most papers.

REFLUX NEPHROPATHY AND PREGNANCY OUTCOMES: SYSTEMATIC REVIEW





ODDS RATIO FOR CAESAREAN SECTION IN REFLUX NEPHROPATHY VERSUS LOW RISK CONTROLS (TOCOS STUDY)

	Reflux nephr	opathy	Low-risk co	ontrols		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
North 2000	28	54	379	1418	49.7%	2.95 [1.71, 5.10]	
Roihuvuo-Leskinen 2015	20	87	379	1418	50.3%	0.82 [0.49, 1.37]	
Total (95% CI)		141		2836	100.0%	1.55 [0.44, 5.46]	
Total events	48		758				

ODDS RATIO FOR PREGNANCY-INDUCED HYPERTENSION IN REFLUX NEPHROPATHY VERSUS LOW RISK CONTROLS (TOCOS STUDY)

	Reflux nephr	opathy	Low-risk co	ntrols		Odds Ratio			2		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	1	М-Н,	Random, 9	5% CI	
North 2000	9	54	66	1418	34.5%	4.10 [1.92, 8.74]			-	-	
Roihuvuo-Leskinen 2015	21	87	66	1418	65.5%	6.52 [3.76, 11.29]					
Total (95% CI)		141		2836	100.0%	5.55 [3.56, 8.66]				•	
Total events	30		132								
Heterogeneity: Tau ² = 0.00	; Chi ² = 0.95, df	= 1 (P = 0	0.33); l² = 0%				L	01		10	100
Test for overall effect: Z = 7	7.55 (P < 0.0000	1)					0.01	0.1	1	10	100

ODDS RATIO FOR PREECLAMPSIA IN REFLUX NEPHROPATHY VERSUS LOW RISK CONTROLS (TOCOS STUDY)

	Reflux nephr	opathy	Low-risk co	ontrols		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	1	М-Н,	Random, 95	5% CI	
Beetz 2002	2	46	25	1418	12.6%	2.53 [0.58, 11.03]			-		
Köhler 2003	18	242	25	1418	17.1%	4.48 [2.40, 8.34]				•	
Marchand 2007	0	242	25	1418	6.8%	0.11 [0.01, 1.86]	•				
Mor 2003	7	47	25	1418	15.8%	9.75 [3.98, 23.87]					
Nisal 2013	8	24	25	1418	15.6%	27.86 [10.92, 71.06]					<u> </u>
North 2000	13	54	25	1418	16.6%	17.67 [8.44, 36.98]					-
Roihuvuo-Leskinen 2015	6	87	25	1418	15.6%	4.13 [1.65, 10.34]				•	
Total (95% CI)		742		9926	100.0%	6.04 [2.41, 15.13]			-		
Total events	54		175								
Heterogeneity: Tau ² = 1.18	3; Chi ² = 37.26, d	f=6(P<	: 0.00001); l ² =	= 84%				-		10	400
Test for overall effect: Z = 3	3.84 (P = 0.0001)	653				0.01	0.1	1	10	100

ODDS RATIO FOR PRETERM DELIVERY IN REFLUX NEPHROPATHY VERSUS LOW RISK CONTROLS (TOCOS STUDY)

	Reflux nephr	opathy	Low-risk co	ontrols		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl		
Köhler 2003	8	242	89	1418	21.4%	0.51 [0.24, 1.07]			
Marchand 2007	1	204	89	1418	15.5%	0.07 [0.01, 0.53]			
Mor 2003	4	47	89	1418	20.1%	1.39 [0.49, 3.96]			
North 2000	17	54	89	1418	21.8%	6.86 [3.72, 12.67]			
Roihuvuo-Leskinen 2015	8	87	89	1418	21.3%	1.51 [0.71, 3.23]			

				- D	12			1922 1920	2023						
Heterogeneity: Tau ² = 0.75; Chi ² = 11.31, df = 1 (P = 0.0008); l ² = 91% Test for overall effect: Z = 0.68 (P = 0.50)	0.01	0.1	1	10	100	Total (95% CI)		634		7090 100.0%	1.03 [0.26, 4.05]				
						Total events	38		445						725
						Heterogeneity: Tau ² = 2.15; Cl Test for overall effect: Z = 0.04	hi² = 49.27, df 4 (P = 0.97)	= 4 (P < 0.0	00001); l² :	= 92%	0.01	0.1	1	10	100

Conclusions:	Reflux nephropathy is associated with an increased risk of PIH and PE, but not of preterm delivery, suggesting the occurrence of late 'maternal' PE, that affect foetal growth and pregnancy outcomes less severely than early 'placental' PE. The finding of a higher incidence of stillbirth in one series demands further analysis. The case reports focused on severe to extreme hydronephrosis, thereby suggesting that regular ultrasounds may be useful in pregnancy. These results suggest the need for focusing follow-up in particular on the last phases of pregnancy, due to the clustering of most of the adverse events (late PE and PIH, stillbirth and possible also hydronephrosis) in these periods.
<section-header></section-header>	 Roihuvuo-Leskinen HM, Vainio MI, Niskanen KM, Lahdes-Vasama TT. Pregnancies in women with childhood vesicoureteral reflux. Acta Obstet Gynecol Scand 2015;94(8):847-51. Nisal M, Hall M, Carr S. Pregnancy in reflux nephropathy: Our experience. BJOG 2013;120 (SUPPL. 3):49. (abstract) Marchand M, Kuffer F, Tonz M. Long-term outcome in women who underwent anti-reflux surgery in childhood. J Pediatr Urol. 2007;3(3):178-83. Mor Y, Leibovitch I, Zalts R, Lotan D, Jonas P, Ramon J. Analysis of the long-term outcome of surgically corrected vesico-ureteric reflux. BJU Int 2003;92(1):97-100. Kohler JR, Tencer J, Thysell H, Forsberg L, Hellstrom M. Long-term effects of reflux nephropathy on blood pressure and renal function in adults. Nephron Clin Practice. 2003;93(1):C35-46. Beetz R, Mannhardt W, Fisch M, Stein R, Thuroff JW. Long-term followup of 158 young adults surgically treated for vesicoureteral reflux in childhood: the ongoing risk of urinary tract infections. J Urol. 2002; 168(2):704-7; discussion 7. North RA, Taylor RS, Gunn TR. Pregnancy outcome in women with reflux nephropathy and the inheritance of vesico-ureteric reflux. Aust N Z J Obstet Gynaecol. 2000;40(3):280-5.



