Supplementary material: Appendix 1-2-3

Disease-modifying anti-rheumatic drug use in pregnant women with rheumatic diseases: a systematic review of the risk of congenital malformations

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Appendix 1. Search Concepts and Corresponding Headings and Keywords

Subject Headings	Text Words*
Concept 1: Arthritis	
▪ exp Arthritis ▪ exp Lupus Erythematosus, Systemic	▪ arthritis ▪ lupus ▪ spondylarthropath*
Concept 2: Pregnancy	
▪ exp Pregnancy ▪ exp Pregnancy Complications ▪	▪ pregnanc* OR pregnant ▪
Concept 3: DMARDs	
▪ exp Antirheumatic Agents ▪ exp Pregnancy Complications	▪ "anti-inflammatory agent*" OR auranofin* OR aurothiglucose* OR chloroquine* OR hydroxychloroquine* OR cyclophosphamine* OR cyclosporin* OR gold salt OR gold salts OR gold sodium thiomalate* OR gold sodium thiosulfate* OR leflunomide* OR methotrexate* OR minocycline* OR prospidium* OR sulfasalizine* OR sulphasalizine* OR sulfasalazine* OR sulphasalazine* OR pencillamine* OR penicillamine* OR "biological agent*" OR adalimumab OR etanercept OR golimumab OR infliximab OR rituximab ▪ "disease modifying antirheumatic*" OR "disease-modifying antirheumatic*" OR "disease modifying anti rheumatic*" OR "disease-modifying anti rheumatic*" OR "disease modifying anti-rheumatic*" OR "disease-modifying anti-rheumatic*" OR DMARD OR DMARDs OR antirheumatic agent* OR anti rheumatic agent* OR anti-rheumatic agent* OR anti rheumatic drug* OR anti rheumatic drug* OR anti-rheumatic drug* ▪ "interleukin 1 receptor antagonist protein" OR "interleukin-4" ▪
Concept 4: Congenital	
▪ exp Congenital Abnormalities ▪ Congenital [Subheading]	▪ congenital ▪ birth defect*
Concept 5: Outcomes	

Subject Headings	Text Words*
▪ exp "Outcome and Process Assessment (Health Care)" ▪ Pregnancy Outcome ▪ exp Risk ▪ (Adverse Effects OR Complications OR Congenital OR Contraindications OR Toxicity) [Subheading]	▪ outcome* ▪ adverse ▪ risk OR risks ▪ prognosis OR prognostic ▪ complication*
Concept 6: Study Types	
▪ Meta-Analysis As Topic ▪ Meta Analysis [Publication Type] ▪ Review Literature As Topic ▪ (Review OR "Review, Academic") [Publication Type] ▪ Randomized Controlled Trial [Publication Type] ▪ Controlled Clinical Trial [Publication Type] ▪ Exp Clinical Trial ▪ Cohort Studies ▪ Exp Case-Control Studies ▪ Exp Longitudinal Studies ▪ Retrospective Studies ▪ Practice Guideline ▪ (Consensus Development Conference OR Consensus Development Conference Nih OR Guideline OR Practice Guideline) [Publication Type] ▪ Evidence-Based Medicine	▪ met analy*" OR metaanaly* OR metanaly* ▪ systematic (review* OR overview*) ▪ quantitative (review* OR overview*) ▪ methodogic* (review* OR overview*) ▪ quantitative (synthesis OR syntheses) ▪ integrative research review* ▪ research integration ▪ random* OR placebo* OR single blind* OR double blind* OR triple blind* ▪ controlled clinical trial* OR controled clinical trial* OR controlled trial* OR controled trial* ▪ cohort* ▪ case (control* OR series OR report* OR study OR studies) ▪ (longitudinal OR follow-up OR follow up OR prospective OR retrospective OR observational) (study OR studies) ▪ CPG OR CPGs OR practice guideline* ▪ evidence based

Appendix 2: Case Reports on Traditional and Biologic DMARD Use During Pregnancy and Congenital Malformation Outcomes

Study	Country	Disease	Exposure				Outcomes		
			DMARD	Dose/Timing in pregnancy	Other Drug(s)	No. of infants	Congenital malformation (Y/N)	Type of malformation*	Other outcomes reported
Pregnancies Exposed to a Single DMARD									
Matz,1968 [15]	USA	SLE	CQ [D1]	250mg BID, 1st trimester	-	3	**Y**	Hearing loss/seizures/ependymoma, hearing-loss/Wilms tumour	SA
Keeling, 2009 [21]	Canada	SLE	HCQ [D1]	not reported	GC	1	N	-	PM
Stirnemann, 2002 [19]	France	SLE	HCQ [D1]	400mg daily, all trimesters	GC, ASA, LMWH	1	N	-	-
Ostensen 2005 [49]	Switzerland	RA	SSZ [DD]	2g BID, all trimesters	GC	1	N	-	-
Williamson,1981[51]	USA	SLE	AZA [D1]	50mg QID	GC	1	**Y**	Pre-axial Polydactyly	PM, CS
Ostrer,1984 [52]	USA	SLE	AZA [D1]	100-150mg/day, 34 weeks	GC	1	**Y**	Micropenis, microcephaly, dysmorphia	PM
Rogers,1980 [47]	Australia	RA	Gold [D1]	20mg q2 weeks, 20 weeks	-	1	**Y**	Hypertelorism, occipital encephalocele, cleft lip/palate	PM, CS
Solomon,1977 [72]	South Africa	RA	D-Pen [D1]	900mg/day, 16 weeks	-	1	**Y**	Dysmorphia, bilateral inguinal hernia, flexion contractures, simian creases	SGA, CS, neonatal death
Somalanka, 2009 [85]	UK	SLE	MMF [D1]	1g BID, 13 weeks	GC, ARB	1	**Y**	Non-communicating duplication of esophagus	PM, sepsis
Corona, 2010 [75]	Mexico	SLE	MTX [D1]	5mg/day, week 5		1	**Y**	Multiple – cranial, facial abnormalities, short thorax, umbilical hernia, coronal hypospadias, cryptorchidism, short limbs, digits, generalized hypotonia, seizures.	PM, CS

Delatycki, 2005 [74]	Australia	RA	MTX **D1**	12.5mg/week, 6 weeks	-	1	**Y**	Developmental delay/seizures	PM
Piggott, 2011 [76]	USA	SLE	MTX **D1**	not reported	-	1	**Y**	Pulmonary atresia, VSD, intestinal malrotation, absent external auditory canal, micrognathia, multicystic kidney	PM
Buckley, 1997 [73]	USA	JIA	MTX **D1**	12.5mg/day, 8 weeks	NSAID	1	**Y**	VSD, double-outlet right ventricle, PA stenosis, skeletal abnormalities	PM
Feldkamp, 1993 [72]	USA	RA	MTX **D1**	7.5mg/week, 2 weeks	NSAID, ASA, misoprostol	1	N	-	PM, CS
Heine, 2008 [82]	Germany	JIA	LEF **D1**	12 weeks pre-conception; serum level 0.5mg/l^{-1} after wash-out	-	1	**Y**	Uncomplicated sacral dysplasia, PDA, VSD, ASD	PM, CS
Enns,1999 [65]	USA	SLE	CTX **D1**	20mg/kg, week 6	GC, ASA	1	**Y**	Multiple – Cranial abnormalities, coronal, facial abnormalities, hypoplastic thumbs, absent/abnormal digits.	-
Kirshon,1988 [64]	USA	SLE	CTX **D1**	200mg IV, weeks 2, 6	GC	1	**Y**	Multiple – Dysmorphic facies, limb abnormalities, generalized hypotonia, developmental delay.	-
Lazalde, 2012 [68]	Mexico	SLE	CTX **D1**	1.4g/m^2, weeks 4, 9	GC	1	**Y**	Dysmorphia, bilateral thumb agenesis, proximal hypospadias, bilateral cryptorchidism, hearing loss	SGA, CS
Aslan, 2005 [66]	Turkey	SLE	CTX **DD**	500mg IV/month week 22, 26	GC	1	N	-	PM, CS
Escobar, 2011 [67]	Columbia	SLE	CTX **D1** HCQ **D1**	125mg/day; 150mg/day	GC	1	N	-	PM, CS

Carter, 2006 [87]	USA	PsA	ETA **D1**	50mg twice weekly, all trimesters	NSAID	1	**Y**	VATER	-
Andrulonis,2012 [93]	USA	PsA	UST **D1**	dose not reported, week 6	-	1	N	-	-
Pregnancy Exposed to Combination of DMARDs									
Streit 2009 [22]	Switzerland	SLE	AZA **D2** HCQ **D2**	dose not reported, week 5	Bosentan, phenprocoumon	1	N	-	CS
Anderka 2009 [20]	USA	SLE	MMF **D1** HCQ **D2**	1g BID, 12 weeks; HCQ not reported	GC, ARB	1	**Y**	Bilateral microtia/hearing loss, bilateral inguinal hernia, tethered foreskin	PM, SGA
Schoner 2008 [53]	Germany	SLE	MMF **D1** AZA **D2**	750mg BID, 8 weeks; 50mg BID, 8 weeks until delivery	-	1	**Y**	Multiple – cranial abnormalities, facial abnormalities, esophageal atresia, abnormal limbs and digits.	TA
Airo, 2002 [18]	Italy	SLE	CSP **D1** HCQ **D2**	3mg/kg/day; 200-400 mg/day	GC, IVIG	1	N	-	PM, SGA

Abbreviations

D1 – Indicates primary drug of interest studied;
D2 – Indicates that drug is concomitant to a primary drug studied;
DM – Indicates *multiple* drugs studied or reported in single paper including particular drug;
DD – Indicates primary disease(s) studied with reporting of exposure to particular drug;

Drugs: ARB – angiotensin receptor blocker; ASA – aspirin; AZA – azathioprine; CQ – chloroquine; CTX – cyclophosphamide; CSP – cyclosporine; D-PEN – D-penicillamine; ETA – etanercept; GC – glucocorticoids; HCQ – hydroxychloroquine; LEF – leflunomide; LMWH – low molecular weight heparin; MMF – Mycophenolate mofetil; MTX – methotrexate; NSAID – non-steroidal anti-inflammatory; SSZ – sulfasalazine; UST – Ustekinumab

Diseases: JIA – juvenile idiopathic arthritis; PsA – psoriatic arthritis; RA – rheumatoid arthritis; SLE – systemic lupus erythematosus.

Outcomes: CS – C-section; PM – premature; SA – spontaneous abortion; SGA – small for gestational age; TA – therapeutic abortion

Appendix 3: Case Series on Traditional and Biologic DMARD Use During Pregnancy and Congenital Malformation Outcomes

Study	Country	Disease (N)	Exposed Pregnancies (N)	Exposure DMARD(s)	Other drug(s)	Outcomes Live births (N)	Congenital malformation (Y/N)	Type of malformation	Other outcomes reported
Pregnancies Exposed to a Single DMARD									
Parke,1988 [16]	USA	SLE, 14	15	CQ [D1] HCQ [D1]	-	7	N	-	4 SA 4 SB
Parke,1996 [25]	USA	SLE, 9	9	HCQ [D2]	8 GC, 2 ASA, 1 heparin	9	N	-	5 PM
Sharon,1974 [54]	USA	SLE, 5	5 (1 set twins)	AZA [D1]	3 GC	4	N	-	1 SA 1 TA 2 PM 1 SGA
Hussein,1993 [63]	Saudi Arabia	SLE, 2	2	CSP [D1]	1 GC	2	N	-	1 PM 1 CS
Ostensen, 2000 [77]	Norway	RA, 2 PsA, 1 JIA, 1*	4	MTX [D1]	1 NSAID	3	N	-	1 SA*
Hajdyla-Banas, 2009 [83]	Poland	RA, 2	2	LEF [D1]	-	2	N	-	-
Scioscia, 2011 [89]	Italy	RA, 2	2	ETA [D1]	-	2	N	-	-
Roux, 2007 [88]	France	RA, 3	3	ETA [D1] ADA [D1]	1 GC	2	N	-	1 TA 1 PM
Pregnancies Exposed to Single or Combination of DMARDs									
Levy, 1991 [17]	Canada	SLE, 10 RA, 1; SLE, 2 RA, 1 **SLE, 1**	11 3 1 **1**	**CQ** [D1] **HCQ** [D1] **CQ** [D1] AZA [D2] **CQ** [D1] **D-Pen** [D2]	8 GC, 1 NSAID 2 GC GC, Phenytoin **ASA**	6 3 1 **1**	N N N **N**	- **-** -	3 SA 1 SB (SLE) 1 SA
Almarzouqi, 2007 [27]	Canada	20 RA	12	**GOLD** [D1]	-	9 (twins)	Y Y	1 tear duct blockage 1 extra-ocular muscle weakness	4 SA 1 SGA

			6	**GOLD** [D1], HCQ [D2]	-	5	N	1 SA
			1	**GOLD** [D1], SSZ [D2]	-	1	N	- -
			1	**GOLD** [D1], HCQ [D2], ETA [D2]	-	1	N	- -
Donnenfeld,1994 [24]	USA	7 RA	6	**MTX** [D1]	1 ASA	3	N	- 3 SA
			1	**MTX** [D1], HCQ ETA [D2]	-	1	N	- -
Kozlowski,1990 [23]	USA	8 RA 1 JIA 1 AA	3	**MTX** [D1]	GC in one, remaining not reported	0	N	- 1 SA 2 TA
			7	**MTX** [D1], HCQ [D2]	6 GC, 4 NSAID, 6 ASA	5 (twins)	N	- 3 SA
Clowse, 2005 [55]	USA	4 SLE	2	**CTX** [D1]	2 GC, 1 ACEi, ARB	0	N	- 2 SA
			1	**CTX** [D1], AZA [D2]	GC	0	N	- 1 FD
			1	**CTX** [D1], AZA [D2], HCQ [D2]	GC, ASA	0	N	- 1 FD
Pregnancies Exposed to Combination of DMARDs								
Lannes, 2011 [28]	Brazil	4 SLE	4	**CTX** [D1], HCQ [D2]	GC	2	N	- 2 SA
		1 SLE	1	**CTX** [D1], AZA [D2]	GC	1	N	- 1 PM
Rosner, 2007 [56]	Israel	2 RA, 1 JIA,	3	**IFX** [D1], AZA [D2]	-	3	N	- 1 PM, 1 CS
		1 SLE	1	**ETA** [D1], MMF [D2]	-			

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