Online Suppplement: Biologicals in atopic disease in pregnancy: an EAACI position paper

Birgit Pfaller[1], Juan José Yepes-Nuñez[2], Ioana Agache[3], Cezmi A. Akdis[4], Mohammad Alsalamah [5,6], Sevim Bavbek[7] Apostolos Bossios[8,9], Onur Boyman [10,11], Adam Chaker[12], Susan Chan[13, 14], Alexia Chatzipetrou[15], George du Toit[16], Marek Jutel[17], Paula Kauppi[18], Antonios Kolios[10,11], Carmen Li[5], Andrea Matucci[19], Alanna Marson[5], Sarah Bendien[20], Oscar Palomares[21], Barbara Rogala[22], Zsolt Szepfalusi[23], Eva Untersmayr[24], Alessandra Vultaggio[19], Thomas Eiwegger [5,25,26]

Short title: EAACI position paper on Biologicals in pregnancy

[1] Department of Medicine, Division of Cardiology, University of Toronto Pregnancy and Heart Disease Research Program, Mount Sinai and Toronto General Hospitals, Toronto, Ontario, Canada

[2] School of Medicine, Universidad de los Andes, Bogotá, D.C., Colombia

[3] Transylvania University Brasov, Faculty of Medicine, Department of Allergy and Clinical Immunology, Brasov, Romania

[4] Swiss Institute of Allergy and Asthma Research (SIAF), Herman-Burchard Strasse 9, 7265 Davos, Switzerland.

[5] Division of Immunology and Allergy, Food Allergy and Anaphylaxis Program, The Hospital for Sick Children, Departments of Paediatrics and Immunology, University of Toronto, Toronto, ON, Canada

[6] College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; Clinical Immunology and Allergy Division, Pediatrics Department, King Abdullah Specialists Children's Hospital, Riyadh, Saudi Arabia

[7] Ankara University, School of Medicine, Department of Chest Disease, Division of Immunology and Allergy, Ankara, Turkey

[8] Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Huddinge, and Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden

[9] Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden

[10] Department of Immunology, University Hospital Zurich, Zurich, Switzerland

[11] Faculty of Medicine, University of Zurich, Zurich, Switzerland

[12]Technical University of Munich, TUM School of Medicine, Klinikum rechts der Isar, Department of Otolaryngology and Center for Allergy and Environment, Munich, Germany

[13] Guy's and St. Thomas' NHS Foundation Trust, Westminster Bridge Road, London, SE1 7EH, United Kingdom

[14] King's College London School of Life Course Sciences & School of Immunology & Microbial Sciences, King's Health Partners, United Kingdom

[15] Allergy Unit 'D. Kalogeromitros', 2nd Department of Dermatology and Venereology, 'Attikon' University Hospital, Medical School, University of Athens, Athens, Greece

[16] Paediatric Allergy Group, Department of Women and Children's Health, King's College London, London, United Kingdom and Paediatric Allergy Group, Peter Gorer Dept of Immunobiology, School of Immunology & Microbial Sciences, King's College London, Guys' Hospital, London, United Kingdom and Children's Allergy Service, Evelina Children's Hospital, Guy's and St. Thomas' Hospital NHS Foundation Trust, London United Kingdom; Asthma UK Centre in Allergic Mechanisms of Asthma, London, United Kingdom

[17] Department of Clinical Immunology, Wroclaw Medical University, Wrocław, Poland; ALL-MED Medical Research Institute; Wroclaw, Poland

[18] Department of Allergy, Skin and Allergy Hospital, Inflammation Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[19] Immunoallergology Unit, Careggi University Hospital, Florence, Italy

[20] Department of respiratory medicine, Haga Teaching Hospital, The Hague, The Netherlands

[21] Department of Biochemistry and Molecular Biology, Chemistry School, Complutense University of Madrid, Spain

[22] Department of Internal Diseases, Allergology & Clinical Immunology Medical University of Silesia, Katowice, Poland

[23] Division of Ped. Pulmonology, Allergology and Endocrinology, Dpt. of Pediatrics, Medical University of Vienna, Austria

[24] Institute of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Austria

[25] Department of Immunology, University of Toronto, Toronto, ON, Canada

[26] Translational Medicine Program, Research Institute, Hospital for Sick Children, Toronto, ON, Canada,

www.eaaci.org

Corresponding Author: Thomas Eiwegger, MD, Division of Immunology and Allergy, Food allergy and Anaphylaxis Program, The Department of Paediatrics, Hospital for Sick Children, 555 University Ave, Toronto, Canada, E-mail: thomas.eiwegger@sickkids.ca, Tel.: + 1416-813-76541862

Tables:

Table S1: Search Strategy

Table S2: Summary of Risk of Bias in non randomized trials

Table S1. Example Search Strategy

MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R) 1946 till April 2018

#	Searches
1	exp Asthma/
2	exp Hypersensitivity, Immediate/
3	hypereosinophilic syndrome/ or pulmonary eosinophilia/
4	("allerg*" or "anaphylactic*" or "anaphylaxis" or "asthma*" or "atopic*" or "atopy*" or "conjunctiviti*" or "dermatiti*" or "eczema*" or "endocarditi*" or "eosinophili*" or "erethism" or "esophagiti*" or "hive*" or "hyper respons*" or "hypereosinophilic" or "hypererg*" or "hypersensibilit*" or "hypersensitiv*" or "keratoconjunctiviti*" or "neurodermatiti*" or "rhiniti*" or "rhinosinusiti*" or "urticaria*" or "weal" or "weals" or "wheal*").tw,kf.
5	1 or 2 or 3 or 4
6	((tumor necrosis factor or TNF) adj3 (inhibit* or block* or anti*)).mp.
7	(biologics or biologicals).mp.
8	exp Antibodies, Monoclonal/
9	((monoclonal or clonal or hybridoma) adj3 (anti bod* or antibod*)).mp.
10	canakinumab.mp.
11	rilonacept.mp.
12	altrakincept.mp.
13	anakinra.mp.
14	pascolizumab.mp.
15	vak694.mp.
16	vak 694.mp.
17	qbx258.mp.
18	qbx 258.mp.
19	amg317.mp.
20	amg 317.mp.
21	dupilumab.mp.
22	pitrakinra.mp.
23	mepolizumab.mp.
24	reslizumab.mp.
25	benralizumab.mp.
26	enokizumab.mp.
27	ustekinumab.mp.
28	anrkinzumab.mp.
29	dectrekumab.mp.
30	lebrikizumab.mp.
31	rpc4046.mp.
32	rpc 4046.mp.

33	gsk679586.mp.
34	gsk 679586.mp.
35	ima026.mp.
36	"ima 026".mp.
37	tralokinumab.mp.
38	secukinumab.mp.
39	ixekizumab.mp.
40	brodalumab.mp.
41	fezakinumab.mp.
42	bms981164.mp.
43	bms 981164.mp.
44	lenzilumab.mp.
45	amg157.mp.
46	amg 157.mp.
47	tocilizumab.mp.
48	omalizumab.mp.
49	ligelizumab.mp.
50	medi4212.mp.
51	medi 4212.mp.
52	quilizumab.mp.
53	mogamulizumab.mp.
54	alefacept.mp.
55	efalizumab.mp.
56	rituximab.mp.
57	daclizumab.mp.
58	oxelumab.mp.
59	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58
60	5 and 59
61	exp "congenital, hereditary, and neonatal diseases and abnormalities"/
62	prenatal injuries/ or prenatal exposure delayed effects/
63	exp "Embryonic and Fetal Development"/
64	exp Embryonic Structures/
65	exp Teratogens/
66	Teratogenesis/
67	exp Pregnancy/
68	exp Pregnancy Complications/
69	Maternal Exposure/
70	(pregnan* or prenatal* or antenatal*).mp.

71	(teratogen* or embryo* or foetus* or fetus* or foetal or fetal).mp.
72	((birth or congenital) adj4 (defect* or malform* or anomal* or abnormal*)).mp.
73	(maternal adj4 expos*).mp.
74	((premature or preterm or pre-term) adj7 (birth* or infan* or child* or baby* or babies or neonat* or deliver* or labour* or labor*)).mp.
75	(low adj3 (birth weigh* or birthweigh*)).mp.
76	(small adj3 (gestation* or date* or age)).mp.
77	(miscarriage* or abortion*).mp.
78	(still born* or stillborn* or stillbirth* or stillbirth*).mp.
79	61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78
80	60 and 79
81	("20170512" or "20170515" or "20170516" or "20170517" or "20170518" or "20170519" or "20170522" or "20170523" or "20170524" or "20170525" or "20170526" or "20170529" or "20170530" or "20170531").ed.
82	(201706* or 201707* or 201708* or 201709* or 201710* or 201711* or 201712* or 2018*).ed.
83	("2017 05 11 0600" or "2017 05 12 0600" or "2017 05 13 0600" or "2017 05 14 0600" or "2017 05 15 0600" or "2017 05 16 0600" or "2017 05 17 0600" or "2017 05 18 0600" or "2017 05 19 0600" or "2017 05 19 0601" or "2017 05 20 0600" or "2017 05 21 0600" or "2017 05 22 0600" or "2017 05 23 0600" or "2017 05 23 0601" or "2017 05 24 0600" or "2017 05 25 0600" or "2017 05 26 0600" or "2017 05 26 0601" or "2017 05 27 0600" or "2017 05 27 0601" or "2017 05 28 0600" or "2017 05 29 0600" or "2017 05 30 0600" or "2017 05 30 0601" or "2017 05 31 0600" or "2017 05 31 0601").dt.
84	("2017 06*" or "2017 07*" or "2017 08*" or "2017 09*" or "2017 10*" or "2017 11*" or "2017 12*" or "2018*").dt.
85	or/81-84
86	80 and 85
87	remove duplicates from 86

Table S2 Online Supplement. Summary of Risk of Bias in *non-randomized studies*.

1. Cortese 2013

Type of study: Case report
Participants: Pregnant woman with severe allergic asthma
Experimental intervention: Omalizumab
Control intervention: none

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Critical[6]	No information[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Critical[6]	No information[7]	**CRITICAL**
Spontaneous abortions (SA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Critical[6]	No information[7]	**CRITICAL**
Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Critical[6]	No information[7]	**CRITICAL**
Small for gestational age (SGA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Critical[6]	No information[7]	**CRITICAL**
Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Critical[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Critical[6]	No information[7]	**CRITICAL**

Explanatory Footnotes

1. Bias due to confounding as confounding inherently was not controllable.
2. Bias due to selection of participants into the study as selection into the study was very strongly related to intervention and outcome; and this could not be adjusted for in analyses.
3. Bias due to classification of interventions as major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.
4. Bias due to deviations from intended interventions since no information is reported on whether there is deviation from the intended intervention.
5. Bias due to missing data since no information is reported about missing data or the potential for data to be missing
6. Bias in measurement of outcomes since the methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.
7. There is too little information to make a judgement

2. Cuervo-Pardo 2016

Type of study: Case series
Participants: Pregnant women with resistant urticaria
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Spontaneous abortions (SA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Small for gestational age (SGA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**

Explanatory Footnotes

1. Bias due to confounding as confounding inherently was not controllable.
2. Bias due to selection of participants into the study as selection into the study was very strongly related to intervention and outcome; and this could not be adjusted for in analyses.
3. Bias due to classification of interventions as major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.
4. No information is reported on whether there is deviation from the intended intervention.
5. Bias due to missing data since no information is reported about missing data or the potential for data to be missing
6. Bias in measurement of outcomes since the outcome measure was subjective and, likely, the outcome was assessed by assessors aware of the intervention received by study participants.
7. There is too little information to make a judgement

3. Danilycheva 2016

Type of study: Case report
Participants: Pregnant woman with chronic inducible urticaria
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Spontaneous abortions (SA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Small for gestational age (SGA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**

Explanatory Footnotes

1. Bias due to confounding as confounding inherently was not controllable.
2. Bias due to selection of participants into the study as selection into the study was very strongly related to intervention and outcome; and this could not be adjusted for in analyses.
3. Bias due to classification of interventions as major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.
4. No information is reported on whether there is deviation from the intended intervention.
5. Bias due to missing data since no information is reported about missing data or the potential for data to be missing
6. Bias in measurement of outcomes since the outcome measure was subjective and, likely, the outcome was assessed by assessors aware of the intervention received by study participants.
7. There is too little information to make a judgement

4. Ghazanfar 2015

Type of study: Case report
Participants: Pregnant woman with chronic spontaneous urticaria with angioedema, atopic dermatitis, and asthma
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Spontaneous abortions (SA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Small for gestational age (SGA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**

Explanatory Footnotes

1. Bias due to confounding as confounding inherently was not controllable.
2. Bias due to selection of participants into the study as selection into the study was very strongly related to intervention and outcome; and this could not be adjusted for in analyses.
3. Bias due to classification of interventions as major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.
4. No information is reported on whether there is deviation from the intended intervention.
5. Bias due to missing data since no information is reported about missing data or the potential for data to be missing
6. Bias in measurement of outcomes since the outcome measure was done using no validated urticaria activity scores.
7. There is too little information to make a judgement

5. Gonzalez-Medina 2017

Type of study: Case reports
Participants: Pregnant women with chronic spontaneous urticaria
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
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Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
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Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**

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4. No information is reported on whether there is deviation from the intended intervention.
5. Bias due to missing data since no information is reported about missing data or the potential for data to be missing
6. Bias in measurement of outcomes since the outcome measure was subjective and, likely, the outcome was assessed by assessors aware of the intervention received by study participants.
7. There is too little information to make a judgement

6. Hirashima 2012

Type of study: Case report
Participants: Pregnant woman with severe asthma
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
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Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**

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4. No information is reported on whether there is deviation from the intended intervention.
5. Bias due to missing data since no information is reported about missing data or the potential for data to be missing
6. Bias in measurement of outcomes since, likely, the outcome was assessed by assessors aware of the intervention received by study participants.
7. There is too little information to make a judgement

7. Kuprys-Lipinska 2014

Type of study: Case reports
Participants: Pregnant women with severe asthma
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
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Spontaneous abortions (SA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Small for gestational age (SGA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**

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3. Bias due to classification of interventions as major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.
4. No information is reported on whether there is deviation from the intended intervention.
5. Bias due to missing data since no information is reported about missing data or the potential for data to be missing
6. Bias in measurement of outcomes since there is not report about how the outcome was measures.
7. There is too little information to make a judgement.

8. Kuschnir 2012

Type of study: Case report
Participants: Pregnant woman with severe asthma
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Spontaneous abortions (SA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Small for gestational age (SGA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	No information[6]	No information[7]	**CRITICAL**

Explanatory Footnotes

1. Bias due to confounding as confounding inherently was not controllable.
2. Bias due to selection of participants into the study as selection into the study was very strongly related to intervention and outcome; and this could not be adjusted for in analyses.
3. Bias due to classification of interventions as major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.
4. No information is reported on whether there is deviation from the intended intervention.
5. Bias due to missing data since no information is reported about missing data or the potential for data to be missing
6. Bias in measurement of outcomes since there is not report about how the outcome was measured.
7. There is too little information to make a judgement

9. Namazy 2015

Type of study: Cohort study
Participants: Pregnant women with asthma
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Moderate[3]	No information[4]	Serious [5]	Moderate[6]	Serious[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Moderate[3]	No information[4]	Serious [5]	Serious[6]	Serious[7]	**CRITICAL**
Spontaneous abortions (SA)	Harm	Critical[1]	Critical[2]	Moderate[3]	No information[4]	Serious [5]	Serious[6]	Serious[7]	**CRITICAL**
Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Moderate[3]	No information[4]	Serious [5]	Serious[6]	Serious[7]	**CRITICAL**
Small for gestational age (SGA)	Harm	Critical[1]	Critical[2]	Moderate[3]	No information[4]	Serious [5]	Serious[6]	Serious[7]	**CRITICAL**
Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Moderate[3]	No information[4]	Serious [5]	Serious[6]	Serious[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Moderate[3]	No information[4]	Serious [5]	Serious[6]	Serious[7]	**CRITICAL**

Explanatory Footnotes

1. Bias due to confounding as confounding inherently was not controllable.
2. Bias due to selection of participants into the study as selection into the study was very strongly related to intervention and outcome; and this could not be adjusted for in analyses.
3. Bias due to classification of interventions as intervention status is well defined; and some aspects of the assignments of intervention status were determined retrospectively.
4. No information is reported on whether there is deviation from the intended intervention.
5. Bias due to missing data since the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.
6. Bias in measurement of outcomes since i) The methods of outcome assessment were comparable across intervention groups; and (ii) the outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and (iii) any error in measuring the outcome is only minimally related to intervention status.
7. Bias in selection of the reported result The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results

10. Vieira Dos Santos 2014

Type of study: Case report
Participants: Pregnant woman with chronic urticaria
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Spontaneous abortions (SA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Small for gestational age (SGA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**

Explanatory Footnotes

1. Bias due to confounding as confounding inherently was not controllable.
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5. Bias due to missing data since no information is reported about missing data or the potential for data to be missing
6. Bias in measurement of outcomes since the outcome measure was subjective and, likely, the outcome was assessed by assessors aware of the intervention received by study participants.
7. There is too little information to make a judgement

11. Ensina 2017

Type of study: Case reports
Participants: Pregnant women with chronic urticaria
Experimental intervention: Omalizumab
Control intervention: None

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		Bias due to confounding	*Bias in selection of participants into the study*	*Bias in classification of interventions*	*Bias due to deviations from intended interventions*	*Bias due to missing data*	*Bias in measurement of outcomes*	*Bias in selection of the reported result*	
Live births	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Still births (SB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Spontaneous abortions (SA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Preterm birth (PTB)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Small for gestational age (SGA)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Low birth weight (LBW)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**
Congenital malformation (CM)	Harm	Critical[1]	Critical[2]	Serious[3]	No information[4]	No information[5]	Serious[6]	No information[7]	**CRITICAL**

Explanatory Footnotes

1. Bias due to confounding as confounding inherently was not controllable.
2. Bias due to selection of participants into the study as selection into the study was very strongly related to intervention and outcome; and this could not be adjusted for in analyses.
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7. There is too little information to make a judgement

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Check for updates

DR. BIRGIT PFALLER (Orcid ID : 0000-0002-2721-6624)
PROF. JUAN JOSÉ YEPES-NUÑEZ (Orcid ID : 0000-0002-9912-0031)
PROF. IOANA AGACHE (Orcid ID : 0000-0001-7994-364X)
DR. APOSTOLOS BOSSIOS (Orcid ID : 0000-0002-0494-2690)
PROF. ONUR BOYMAN (Orcid ID : 0000-0001-8279-5545)
PROF. GEORGE DU TOIT (Orcid ID : 0000-0002-0321-2928)
DR. OSCAR PALOMARES (Orcid ID : 0000-0003-4516-0369)
PROF. BARBARA ROGALA (Orcid ID : 0000-0002-3077-0271)
PROF. ZSOLT SZEPFALUSI (Orcid ID : 0000-0003-4852-3102)
DR. EVA UNTERSMAYR (Orcid ID : 0000-0002-1963-499X)
DR. THOMAS EIWEGGER (Orcid ID : 0000-0002-2914-7829)

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Biologicals in atopic disease in pregnancy: an EAACI position paper

Birgit Pfaller[1], Juan José Yepes-Nuñez[2], Ioana Agache[3], Cezmi A. Akdis[4], Mohammad Alsalamah [5,6], Sevim Bavbek[7] Apostolos Bossios[8,9], Onur Boyman [10,11], Adam Chaker[12], Susan Chan[13, 14], Alexia Chatzipetrou[15], George du Toit[16], Marek Jutel[17], Paula Kauppi[18], Antonios Kolios[10,11], Carmen Li[5], Andrea Matucci[19], Alanna Marson[5], Sarah Bendien[20], Oscar Palomares[21], Barbara Rogala[22], Zsolt Szepfalusi[23], Eva Untersmayr[24], Alessandra Vultaggio[19], Thomas Eiwegger [5,25,26]

Short title: EAACI position paper on Biologicals in pregnancy

[1] Department of Medicine, Division of Cardiology, University of Toronto Pregnancy and Heart Disease Research Program, Mount Sinai and Toronto General Hospitals, Toronto, Ontario, Canada

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[2] School of Medicine, Universidad de los Andes, Bogotá, D.C., Colombia

[3] Transylvania University Brasov, Faculty of Medicine, Department of Allergy and Clinical Immunology, Brasov, Romania

[4] Swiss Institute of Allergy and Asthma Research (SIAF), Herman-Burchard Strasse 9, 7265 Davos, Switzerland.

[5] Division of Immunology and Allergy, Food Allergy and Anaphylaxis Program, The Hospital for Sick Children, Departments of Paediatrics and Immunology, University of Toronto, Toronto, ON, Canada

[6] College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; Clinical Immunology and Allergy Division, Pediatrics Department, King Abdullah Specialists Children's Hospital, Riyadh, Saudi Arabia

[7] Ankara University, School of Medicine, Department of Chest Disease, Division of Immunology and Allergy, Ankara, Turkey

[8] Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Huddinge, and Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden

[9] Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden

[10] Department of Immunology, University Hospital Zurich, Zurich, Switzerland

[11] Faculty of Medicine, University of Zurich, Zurich, Switzerland

[12]Technical University of Munich, TUM School of Medicine, Klinikum rechts der Isar, Department of Otolaryngology and Center for Allergy and Environment, Munich, Germany

[13] Guy's and St. Thomas' NHS Foundation Trust, Westminster Bridge Road, London, SE1 7EH, United Kingdom

[14] King's College London School of Life Course Sciences & School of Immunology & Microbial Sciences, King's Health Partners, United Kingdom

[15] Allergy Unit 'D. Kalogeromitros', 2nd Department of Dermatology and Venereology, 'Attikon' University Hospital, Medical School, University of Athens, Athens, Greece

[16] Paediatric Allergy Group, Department of Women and Children's Health, King's College London, London, United Kingdom and Paediatric Allergy Group, Peter Gorer Dept of Immunobiology, School of Immunology & Microbial Sciences, King's College London, Guys' Hospital, London, United

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Kingdom and Children's Allergy Service, Evelina Children's Hospital, Guy's and St. Thomas' Hospital NHS Foundation Trust, London United Kingdom; Asthma UK Centre in Allergic Mechanisms of Asthma, London, United Kingdom

[17] Department of Clinical Immunology, Wroclaw Medical University, Wrocław, Poland; ALL-MED Medical Research Institute; Wroclaw, Poland

[18] Department of Allergy, Skin and Allergy Hospital, Inflammation Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[19] Immunoallergology Unit, Careggi University Hospital, Florence, Italy

[20] Department of respiratory medicine, Haga Teaching Hospital, The Hague, The Netherlands

[21] Department of Biochemistry and Molecular Biology, Chemistry School, Complutense University of Madrid, Spain

[22] Department of Internal Diseases, Allergology & Clinical Immunology Medical University of Silesia, Katowice, Poland

[23] Division of Ped. Pulmonology, Allergology and Endocrinology, Dpt. of Pediatrics, Medical University of Vienna, Austria

[24] Institute of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Austria

[25] Department of Immunology, University of Toronto, Toronto, ON, Canada

[26] Translational Medicine Program, Research Institute, Hospital for Sick Children, Toronto, ON, Canada,

Corresponding Author: Thomas Eiwegger, MD, Division of Immunology and Allergy, Food allergy and Anaphylaxis Program, The Department of Paediatrics, Hospital for Sick Children, 555 University Ave, Toronto, Canada, E-mail: thomas.eiwegger@sickkids.ca, Tel.: + 1416-813-76541862

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Abbreviations

CM = congenital malformation

EAACI = European Academy of Allergy and Clinical Immunology

EMA = European Medicine Agency

ERS = European Respiratory Society

EULAR = European League Against Rheumatism

EXPECT study = observational study of the use and safety of omalizumab

FcRn = neonatal Fc receptors

FDA = Food and Drug administration

GINA = Global Initiative for Asthma

GRADE = Grading of Recommendations Assessment, Development and Evaluation

ICS = inhaled corticosteroids

Ig = immunoglobulin

IL = interleukin

ILC3 = type 3 innate lymphoid cells

LBW = low birth weight

M1 = classically activated macrophages

M2 = alternatively activated macrophages

NRS = non-randomized studies

PTB = preterm birth

RCT = randomised controlled trial

ROB = risk of bias

SGA = small for gestational age

SHARP = Severe Heterogeneous Asthma Research collaboration, Patient-centred

TGF-β = transforming growth factor beta

Th = T helper type

TNF-□ = anti-tumor necrosis factor alpha

Tregs = regulatory T-cells

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TSLP = thymic stromal lymphopoietin

Key words

Allergy, asthma, atopic dermatitis, biologicals, pregnancy

Abstract

Biologicals have transformed the management of severe disease phenotypes in asthma, atopic dermatitis, and chronic spontaneous urticaria. As a result, the number of approved biologicals for the treatment of atopic diseases is continuously increasing. Although atopic diseases are among the most common diseases in the reproductive age, investigations, and information on half-life, pharmacokinetics defining the neonatal Fc receptors (FcRn) and most important safety of biologicals in pregnancy are lacking. Given the complex sequence of immunological events that regulate conception, fetal development, and the intrauterine and postnatal maturation of the immune system, this information is of utmost importance. We conducted a systematic review on biologicals in pregnancy for indications of atopic diseases. Evidence in this field is scare and mainly reserved to reports on the usage of omalizumab. This lack of evidence demands the establishment of a multidisciplinary approach for the management of pregnant women who receive biologicals and multicenter registries for long-term follow-up, drug trial designs suitable for women in the reproductive age, and better experimental models that represent the human situation. Due to the very long half-life of biologicals, pre-conception counseling, and health care provider education is crucial to offer the best care for mother and fetus. This position paper integrates available data on safety of biologicals during pregnancy in atopic diseases via a systematic review with a detailed review on immunological considerations how inhibition of different pathways may impact pregnancy.

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Introduction

Atopic diseases, including food allergy, allergic rhino-conjunctivitis, allergic asthma, atopic dermatitis, and chronic urticaria, affect more than 20% of the general population in developed countries.[1-3] Monoclonal antibodies directed against targets of the immune system, such as cytokines and chemokines and their respective receptors, surface markers and IgE, belong to "biologicals". Initial applications focused on autoimmune disorders (inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, systemic lupus erythematosus, hematopoietic and lymphatic malignancies). For these diseases, biologicals may represent first to third-line treatment options.[4-9] Although data is still limited, the safety profiles of biologicals have been assessed for these conditions pre-conception as well as during pregnancy and while breastfeeding[10-12]. The safety data with respect to teratogenicity of some of the biologicals (e.g. anti-tumor necrosis factor alpha (TNF-□) are encouraging.[13-15] However, there may be more subtle, yet still relevant, implications on the usage of life vaccinations, and infections that demand a closer look. [16-18]

The use of biologicals is typically considered in moderate-to-severe disease phenotypes when conventional treatment approaches prove ineffective or are poorly tolerated.[16,19] Information on the use of biologicals for the treatment of atopic disorders during pregnancy is limited in humans. This results in significant uncertainty at the level of clinical decision making when adequately treated women with good therapeutic response on biologicals become pregnant. Therefore, treatment is often stopped because of the lack of safety data. However, there is a relevant risk that atopic diseases like asthma or allergic rhinitis or food allergy deteriorate during pregnancy[20,21]. Thus, treatment with the optimal regimen is essential for the mother and the child. Moreover, these women usually need a high dose of topical, inhaled, or systemic steroids, which may carry the risk of pre-eclampsia, cleft-palate, pre-term delivery among other complications. It is not known whether a high dose of traditional treatment such as steroid or calcineurin-inhibitors is safer or carries more risk compared to biologicals. Thus, it is of utmost importance to establish data on the safety of biologicals in pregnancy. Currently, the body of evidence is restricted to small datasets and case reports.

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In this position paper, the Task Force on Biologicals in Atopic Disease in Pregnancy aimed to gather existing evidence by performing a systematic review and synthesize that limited knowledge with considerations on potential risks and benefits that come with the application of biologicals in pregnancy.

Structural and mechanistic considerations regarding the placental transfer of biologicals

Targeting immune disorders using biologicals during pregnancy demands the consideration of the immunopharmacology of the pregnant woman, the developing immune system of the child, and the potential impact on the complex and fragile immunological interactions at the feto-maternal interface. Pregnancy results in a multitude of hormonal, metabolic, and physiological changes leading to a higher cardiac output, an increase in plasma volume, decreased concentrations of drug-binding proteins, increased renal clearance, and changed hepatic clearance. All of these alterations affect the activity of the drug.[22] In particular, increased blood flow, increased total body water, and placental distribution and transfer through neonatal Fc receptors (FcRn) might affect the pharmacokinetics of biologicals.[23] It remains unknown whether anti-drug antibody formation is more likely to happen during pregnancy.[23] Biologicals have a high molecular weight with a hydrophilic profile. They have a relatively small volume of distribution and are primarily eliminated by the reticuloendothelial system.[24] Biologicals bind to the MHC class I-related FcRn, which is widely expressed on endothelial, epithelial, and hematopoietic cells. The FcRn is a heterodimer consisting of an alpha chain and the beta-2 microglobulin. It interacts with the CH2/CH3 part of the Fc domain with very high affinity at a pH of 6-6.5 and shows low to absent binding at a pH of 7-7.4. [25] This formation of the FcRn-biological complex protects from degradation and leads to distribution to different tissues. This complex formation is further responsible for the transfer of biologicals to the fetus [26] and the prolonged half-life of IgG compared to other isotypes, and consequently also for the prolonged half-life of biologicals. [27] Since Fc□RI, IIa, IIb, IIIa are also expressed in the term placenta on various cell types, they may as well contribute to IgG transfer. More evidence is needed to estimate their relative contribution. [28]

Pharmacokinetic data during pregnancy for those biologicals approved for atopic disease is needed to understand and treat pregnant women appropriately.

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Approved biologicals for the treatment of atopic disease are either of an IgG1 (omalizumab, mepolizumab, and benralizumab) or IgG4 (reslizumab and dupilumab[29]) isotype. IgG levels in the fetal circulation increase after week 13, reach 50% at weeks 28-32, and may exceed maternal levels after week 35 (Figure 1).[30,31] The precise IgG levels in a fetus depend on the IgG levels of the mother. IgG1 is transported with the highest efficacy, whereas IgG2 remains at levels of about 60% of the maternal concentration. The placental transport is dependent on the Fc portion and efficacy is as follows: IgG1>IgG4>IgG3>IgG2[30]. IgG3 displays a significantly shorter half-life of 7 days compared to 21days for the other isotypes.[32] Due to the dependence on the Fc portion, antibodies like Certolizumab pegol, a targeting humanized monoclonal antibody for the treatment of inflammatory bowel disease, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, which lack the Fc region do not cross the placenta. Due to the immature reticuloendothelial system, reduced clearance of biologicals in infants has been proposed. At the time of the preparation of this systematic review (January 2020), there were no studies published about drug levels in newborn exposed to biologicals approved for atopic disease administered to mothers perinatally, human data have been mostly reported on TNF-□ blockers.[33,34]

Rituximab, a chimeric human-murine anti-CD20 IgG1 monoclonal B cell–depleting antibody has been used in selected cases of atopy to treat eczema[35-37] and idiopathic anaphylaxis [38]. Case reports, case series, and pharmacovigilance data from pre-conception through pregnancy in up to 153 cases with known outcomes for different chronic disorders, primarily malignancies, and rheumatoid arthritis, have been reported. These limited results show no increased risk of congenital malformation compared to the normal population or pregnancies of mothers with chronic disease.[39,40] As anticipated, rituximab causes B-cell depletion. Hematologic abnormalities and low B-cell counts have been reported in newborns. The reported outcomes showed normalization of B-cell counts within a few months of life [39,40].

The role of cytokines in pregnancy – Potential issues for the use of biologicals

Tolerance towards the fetus, while providing adequate and constant protection against potential infections, requires a complex interplay of regulatory and effector immune functions in the placenta and in the overall immune system of the pregnant mother (Figure 2). In the early days of reproductive

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immunology, when the Th1 / Th2 paradigm was first proposed, it was generally accepted that successful pregnancy in humans was associated with a trend towards the type 2 cytokine profile and suppression of the type 1 cytokine profile [41-43]. In line with that theory, numerous studies reported a predominant Th1-type immunity in recurrent spontaneous abortion, preterm birth, and preeclampsia [44-47]. It is now established that a successful pregnancy requires a high level of immune fine-tuning rather than a "Th2 dominant phenomenon".

Implantation and placentation of the human embryo, fetal growth, and labor are considered distinct developmental stages, and the immunological response has to adapt rather than be suppressed to each of these processes[48]. Increased pro-inflammatory chemokines, cytokines, such as TNF-α, Interleukin 6 (IL-6) and IL-1β, and growth factors, active mast cells, dendritic cells, NK cells, monocytes, and M1-macrophages are observed during implantation[49,50]. During placental development, M2-macrophages promote tissue integrity by secreting IL-10 and TGF-β.

There is now substantial evidence that the Th1 cytokines play a role in the initiation of labor at term, driving cervical ripening and myometrial activation[51]. Premature activation of these pathways, for example, by infection, can lead to preterm labor and birth. Fetal membranes[52,53] and myometrium produce IL-1β at term, a potent nuclear factor κB (NF-κB) inducer[54]. Nuclear factor κB regulates the expression of numerous labor-associated genes, including COX-2, the oxytocin receptor, CXCL8, and matrix metalloproteinase-9 (MMP-9) involved in both term and preterm labor [54]. In preterm labor, the secretion of Type-2 and Type 1 cytokines is also elevated [55,56].

IL-5 is a prominent Th2 cytokine, which is closely linked to the development and expansion of eosinophils and their precursors. Eosinophils, which are classically linked to inflammation, may also play a crucial role in maintaining cellular homeostasis by their presence in tissues like the intestine, thymus, and the uterus.[57,58] These are so-called homeostatic eosinophils. IL-5-dependent eosinophils have a longer half-life. In the thymus, eosinophils may contribute to central tolerance[59]. Eosinophils are infiltrating the uterus in a cyclic manner and may impact conception[60]. Eotaxin-deficient animals, with impaired eosinophil recruitment, display a delay in the establishment of the first estrus cycle as well as the first age of parturition.[57] Importantly, this potential impact on fertility could not be substantiated with eosinophil deficient mice that showed normal fertility and reproduction. [61] In the perinatal period, the development of the mammary gland in mice is eosinophil-dependent and impacts

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the growth and development of the weanlings [62 63]. Additional data and confirmation of the relevance of these observations in humans are required. Distinct approaches to target eosinophils, either via antibody-dependent cellular cytotoxicity such as Benralizumab (targeting the IL5R) or via blockage of IL-5, may affect such "beneficial" non-pathogenic eosinophil populations differently and also eliminate other IL5R bearing cell populations such as basophils or ILC2.

Th17 and T regulatory (Tregs) also have to be studied in pregnancy. IL-17A-producing cells such as Th17 cells and type 3 innate lymphoid cells (ILC3) are key components of type 3 immune responses to combat extracellular infections. Aberrant type 3 immune responses are characterized by the overproduction of IL-17A resulting in autoimmune and inflammatory diseases.[64,65] Regulatory T (Treg) cells are capable of controlling excessive inflammation and promoting tolerance.[66] Similar to alterations of type 1 responses, reduced ratios of functional Treg and Th17 cells and other IL-17A-producing cells are associated with differing pregnancy-related morbidities, such as recurrent spontaneous abortions [67,68], pre-eclampsia [69,70], and other co-morbidities such as asthma, autoimmune disease, preterm birth, chorioamnionitis, and gestational diabetes.[71]

Early in pregnancy, local differentiation of Th17 in the reproductive tract and the placenta is very important for a successful pregnancy due to their ability to react in highly regulatory stages in which inflammation could be necessary.[64,71,72] After implantation and before delivering, fetal growth is needed, and anti-inflammatory responses and Treg cells are required. Recurrent spontaneous abortion, defined as two or more consecutive pregnancy losses before 20 weeks, shows significantly higher levels of Th17 cells and the Th17-promoting cytokines IL-23, IL-1β, and IL-6 in peripheral blood and decidua compared to healthy pregnancies [68,71]. Pre-eclampsia could be a dysregulation of the Th17/Th1 and Treg cell responses.[70,71] Collectively, Th17 cells play an essential role during pregnancy, but they are also up-regulated in recurrent spontaneous abortion and pre-eclampsia. Mechanistically, the local and systemic balance between effector type 1/type 2/type 3 cells and regulatory cell subsets is essential for a successful and healthy pregnancy[73] (Figure 2).

Biologicals for atopic diseases and fertility

Studies show increasing evidence for an association between asthma and reduced fertility.[74,75] Actively treated and therefore, better-controlled asthma is suggested to reduce this risk. [74,76] For other

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atopic diseases like atopic dermatitis, the relation with reduced fertility is less clear.[77] The ongoing Pregnancy Rate, Asthma, infertility, Omalizumab (PRO_ART) trial explores differences in the pregnancy rate between asthmatic women receiving treatment with omalizumab compared to "regular" asthma treatment.[78] The hypothesis is that systemic inflammation in asthma possibly results in reduced fertility, and anti-inflammatory therapy may be protective. While the exact mechanisms remain unclear, it is likely that systemic inflammation also affects the uterine mucosal layer (decidua) and thereby impair effective implantation of the embryo.[79,80] Inflammatory cells such as eosinophils are increasingly recognized to play a role in reproductive health, remodeling processes and changes in the reproductive organs during puberty and pregnancy. [81] Currently available biologicals targeting IL-5 and IL-4/IL-13 are effective in reducing eosinophilic inflammation. It is unclear if at all or to what extent these therapies impact fertility. Existing, albeit limited, experience with biologicals for atopic diseases suggests that treatment with these drugs does not reduce the fertility of women and men.[82]

Approved and investigational status of biologicals in atopic disease and pregnancy

Several biologicals targeting cytokines of type 2 inflammation are currently approved for the treatment of atopic disease (Table 1). Mepolizumab, reslizumab (anti-IL-5), and benralizumab (anti-IL-5R□) that target IL-5 are approved for severe eosinophilic asthma and are under investigation for chronic rhinosinusitis with nasal polyposis and eosinophilic esophagitis. The anti-IL-4R□□antibody dupilumab is approved for the treatment of severe atopic dermatitis and type severe asthma and chronic rhinosinusitis with nasal polyposis. Tezepelumab, a biological targeting thymic stromal lymphopoietin (TSLP), is under development for atopic dermatitis (NCT03809663) and a multicenter, randomized, double-blind, placebo-controlled phase 3 study was initiated evaluating the efficacy and safety of tezepelumab for severe uncontrolled asthma in adults (NCT03927157). Etokimab is an anti-IL-33 mAb under investigation for several atopic diseases, including severe asthma (NCT03533751), peanut allergy[83], and chronic rhinosinusitis with nasal polyps (NCT03614923). Biologicals targeting non-cytokines, especially IgE, of interest for atopic disease include omalizumab[84] [85]and ligelizumab[86]. Omalizumab has been approved by the FDA in 2003 and in 2005 by the EMA for asthma. In 2014 the FDA and EMA approved it for chronic spontaneous urticaria (CSU), and it is under investigation for food allergy and chronic rhinosinusitis with nasal polyposis. The FDA issued a warning of

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anaphylaxis up to one year after beginning of omalizumab treatment due to cases of allergic reactions to it. Patients should be informed accordingly. In 2019, the European Public Assessment Report (EPAR) was updated by EMA and states that omalizumab might be considered for use in pregnancy. Ligelizumab/QGE031 is an anti-IgE biological with a 50-fold higher affinity for IgE than omalizumab, and it is in the process of approval for chronic spontaneous urticaria with positive phase 3 data.[86] Further under investigation for atopic disease are nemolizumab (IL-31 receptor α) [NCT03985943], fezakinumab (IL-22)[87], bermekimab (IL-1a) [NCT03496974] and GBR-830 (OX40).[16]

Current international recommendations and safety data of biologicals approved for atopic disease from other disease entities and registries

Current recommendations for the use of biologicals during pregnancy have been published by gastroenterology and rheumatology societies[5,13]. They predominantly address TNF-□ inhibitors used for the treatment of inflammatory bowel disease or rheumatoid arthritis. Data is scarce due to ethical and practical constraints to include pregnant women in randomized controlled interventional studies. This is certainly warranted to protect the mother and the child, but it also results in knowledge gaps and a lack of treatment recommendations for this vulnerable group of patients. TNF-□ inhibitor usage data derive from observational studies, case reports, and animal data. The knowledge of increased transfer in the third trimester and the lack of data on long-term outcomes on the developing fetus leads to different treatment recommendations between societies. The European League Against Rheumatism (EULAR) points to consider for the use of antirheumatic drugs during pregnancy and lactation[88] and advocates for infliximab and adalimumab that it can be given until 20 weeks of gestation and if indicated throughout pregnancy. In the case of rituximab, administration in specific cases may be considered at the beginning of pregnancy. If rituximab is used at later stages of pregnancy, the patient has to be informed about the risk of B-cell depletion and other cytopenias in the neonate. The British Society for Rheumatology and Health Care Professionals[89] recommends infliximab exposure only until 16 weeks of gestation and adalimumab and etanercept until the end of the second trimester. Furthermore, exposure to rituximab, tocilizumab and belimumab is not recommended during the preconception period and in pregnancy[89]. In comparison, the Toronto

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Consensus Report endorses to maintain treatment and only in patients with low relapse risk to discontinue the treatment. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine categories TNF-□ inhibitors as low risk emerging therapies with developing evidence for use during pregnancy, and rituximab and belimumab as an intermediate risk with little or no data[75]. To stop biologicals during pregnancy is based mainly on expert opinions [88,89] and on one fatal case report of an infant exposed to infliximab in utero, which died after BCG vaccination[90].

The currently available guidelines for the treatment of asthma do not provide recommendations for biological use during pregnancy.[91,92] The Global Atlas for Asthma[93] provides information on omalizumab by stating the outcome of the observational study of the use and safety of omalizumab (EXPECT study)[94], whereas it is not addressed in the 2019 updated GINA guidelines. The Scottish and British Clinical Guideline revised in July 2019 states that for immunomodulatory therapy during pregnancy no clinical data is available for moderate-to-severe allergic asthma in pregnancy.[95] The Consensus-based European guidelines for treatment of atopic dermatitis in adults and children reports the only European Medicines Agency (EMA) and Food and Drug Administration (FDA) approved biological for the treatment of atopic dermatitis is dupilumab.[96] No published human data is available for recommendations of dupilumab use in pregnant women with atopic disease. The Australian Handbook for Asthma lists the biologicals omalizumab, mepolizumab, and benralizumab according to the Therapeutic Goods Administration Australian prescribing medicine in pregnancy as Category B1 (Definition: “Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage”.) [97]

This EAACI position paper integrates a systematic review on biologicals in atopic diseases in pregnancy and theoretical considerations on their usage.

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Systematic review on biologicals in atopic diseases in pregnancy

Methods

The Prisma checklist directed the reporting of this systematic review (Figure 3). We registered the protocol in Prospero (registration number CRD42018094401).

Inclusion and exclusion criteria

We included randomized controlled trials (RCT) and non-randomized studies (NRS), specifically cohort studies, case-control studies, and case report studies. Studies had to include pregnant women with atopic disease diagnosed according to disease-related standard criteria and treated with biologicals[20,98-101]. For the purpose of this review 'biologicals' were defined as monoclonal antibodies directed against the following targets: IgE; interleukin-4 (IL-4), IL-5, IL-9, IL-13, IL-31, TSLP, IL-1b, IL-12, IL-17A, IL-17F, IL-23, TNF-□, chemokine receptor CCR4, lymphocyte surface, and adhesion molecules, including CD2, CD11a, CD20, CD25, and OX40 ligand [102].We excluded animal studies, studies not reporting pregnancy outcomes, articles with no description of modalities of treatment, editorial commentaries, and narrative reviews.

Type of outcomes

We investigated the following primary outcomes: live births, preterm birth (defined before 37 weeks of gestation) [PTB], small for gestational age (birth weight < 10th centile for gestation and sex) [SGA], low birth weight (defined as <2.5 kg) [LBW], congenital malformation [CM], stillbirths (fetal loss after 20 weeks) [SB], spontaneous abortions (fetal loss including 'miscarriage' under 20 weeks) [SA]. The secondary composite outcome was neonatal complications [neonatal respiratory distress, neonatal interventricular hemorrhage, neonatal necrotizing enterocolitis, neonatal sepsis], information on child morbidity, and long-term growth and development.

Search methods

We performed our search on MEDLINE (Ovid), Embase (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL) (Ovid), Web of Science (Thomson Reuters), and all three major clinical trials databases: ClinicalTrials.gov (NIH web) (https://clinicaltrials.gov/); International

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Standard Randomized Clinical Trials Number (ISRCTN registry) (www.controlled-trials.com) and the Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au) to identify trials in progress from their inception to the April 2017 and updated one time till April 2018 with no restriction on language of publication. Search strategy reported in the Online Supplement (Suppl. Table 1). We searched conference abstracts, presentations, reference lists of reviewed articles and contacted clinical experts and pharmaceutical companies in the specialty for additional references.

Study selection and data extraction

Three independent evaluators (MA, BP, CL) screened the titles and abstracts obtained through the electronic searches. Two evaluators (BP, CL) assessed the full texts to make a final eligibility decision. In cases of disagreement, a third reviewer (TE) was consulted. If additional information or clarification was needed about a study, we contacted the authors of the relevant article.

A standardized data extraction form was created, and two independent reviewers (BP, CL) extracted the data, and any disagreements between the reviewers were resolved by consensus after further evaluation or by the involvement of a third reviewer (TE).

Assessment of risk of bias

One reviewer (JJYN) assessed the risk of bias for each randomized study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of interventions [103](The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org). For non-randomized studies, he used the Cochrane Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool (Online supplement Table 2). [104]

Data analysis

Two reviewers (BP, CL) independently summarized the data in an extraction form. They discussed disagreements and, if necessary, reached an agreement by consultation with a third reviewer (TE). The reviewers extracted the following information from 11 eligible individual studies. We used Microsoft Excel 16.16.9 for Mac for data management and descriptive information.

GRADE assessment of the overall certainty in the body of evidence by outcome

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We then used the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology to rate the certainty in the body of evidence for each outcome as high, moderate, low, or very low [105106]. The assessment included judgments about risk of bias, imprecision, inconsistency, indirectness, and publication bias[107-109]. We also rated the certainty in the body of evidence using a GRADE approach to observational studies [110]. To assess the usefulness of including NRS, we applied the GRADE NRS framework for when to consider NRS [111]. A methodologist checked all GRADE tables and ratings of the certainty in the body of evidence (JJYN). We created Evidence Profile and Summary of Findings Tables for each population using GRADE's electronic tool GRADEpro GDT (www.gradepro.org)

RESULTS

The search of the MEDLINE, Embase, CENTRAL), Web of Science, and ClinicalTrials.gov yielded 5425 unique records after duplicates were removed. Title and abstract screening by two review authors led to the exclusion of references. Figure 3 shows the PRISMA flow diagram [112]; the full texts of 203 publications have been reviewed, and 191 articles have been excluded. Overall, 12 NRS (1 cohort study, and 11 case reports) met our inclusion criteria[94,113-122]. In total, all 12 publications reported 211 pregnancies exposed to biologicals (omalizumab and rituximab) eight weeks prior to conception or during pregnancy (Table 2). The cohort study [94] stated that out of the included 191 pregnant women all except for three had been exposed in the first trimester (n=188). All pregnancies reported in the case reports had been exposed at least in the first trimester. The one cohort study and four case reports reported pregnancy exposure due to the underlying diagnosis of asthma, six case reports included urticaria patients and one case report indicated biological exposure due to atopic dermatitis. All articles reported on congenital malformations, but the other outcomes of preterm birth, small for gestational age, spontaneous abortion and therapeutic abortion were not consistently stated in all articles. Our search did not reveal any RCTs. One cohort study[94] with 169 pregnancies and 11 case reports with 20 pregnancies reported in total 189 pregnancies with a known outcome. Medical indication for omalizumab exposure was asthma, atopic dermatitis and urticaria. Rituximab led to the successful treatment of one case of atopic dermatitis. The one case report with rituximab exposure

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was a twin pregnancy with delivery of healthy infants at 36 weeks and no hematologic or other adverse effects[122]. All other included studies reported exposure to omalizumab during pregnancy.

Given the off-label indication of rituximab, the following summary of outcomes and GRADE assessment was performed only for omalizumab data (Table 3).

Primary outcomes

Live births: In total, 178 live-births have been reported in 188 pregnancies with known outcomes exposed to omalizumab in women with atopic disease. The cohort study contained 156 live births with 160 infants (4 twins)[94], and 125 full-term from the singleton pregnancies have been reported. 10 NRS reported the effect of biologicals on 18 live births[113-121123]. The overall quality in the body of evidence was very low due to the risk of bias.

Preterm birth (PTB): the cohort study reported on 156 live births and 22 preterm deliveries in the singleton pregnancies and in total 25 preterm deliveries including twins. In the 10 case reports two preterm births were reported. This included one at 26 weeks to threatening abortion resulting in cesarean delivery of a 544g female infant with low birth weight and no long-term difficulties[114]. One woman diagnosed with severe allergic asthma delivered preterm (reported 8 months of gestation) via caesarean delivery after agreement with the obstetrician[113]. The overall quality in the body of evidence was very low due to the risk of bias.

Small for gestational age (SGA): SGA has been reported in 16 infants out of 147 with known birth weight in the cohort study. [94] One SGA infant was reported in a case report[114]. The overall quality in the body of evidence was very low due to the risk of bias.

Low birth weight (LBW): LBW has been reported in 4 infants out of 125 known outcomes in the cohort study. [94] One LBW infant was reported in a case report[114]. The overall quality in the body of evidence was very low due to the risk of bias.

Congenital malformation (CM): Out of the known 178 live births (4 twin pregnancies) were 7 major congenital malformations[94] and in total 20 infants with minor and or major malformations, including cutaneous mastocytosis (n=1), patent foramen ovale (n=1), vesicoureteral reflux (n=1), arteriovenous malformation (n=1), bilateral renal pelvis dilatation (n=1), hypospadias (n=2). Additional conditional malformations have been reported in 14 infants[94]. The overall quality in the body of evidence was very low due to the risk of bias.

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Still births (SB): Only one stillbirth was reported in the EXPECT study [94] out of 169 reported pregnancy outcomes. No stillbirth was reported in the remaining case reports. The overall quality in the body of evidence was very low due to the risk of bias.

Spontaneous abortions (SA): Pregnancy losses in the first trimester have been reported as 12 spontaneous abortions.[94] 11 SA have been reported in the one cohort study [94] out of 169 reported pregnancy outcomes. The overall quality in the body of evidence was very low due to the risk of bias.

Secondary outcomes

Composite secondary outcomes consisted of neonatal respiratory distress, neonatal interventricular hemorrhage, neonatal necrotizing enterocolitis, neonatal sepsis, as well as long-term growth and development. Due to the limited published data, we were unable to report on the neonatal and long-term outcomes of the offspring. However, neonatal complications have been described in two offspring: One woman was diagnosed with preeclampsia and respiratory failure and her infant with neonatal thrombocytopenia.[94] Another woman was diagnosed with a urinary tract infection during labor and delivered at 40 weeks a baby (APGAR 9) with congenital pneumonia, however, after successful treatment, he left the hospital in good medical condition within a week.[115]

Findings from publications outside of the systematic review

We screened all three major clinical trials and located the ongoing randomized, double-blinded, parallel-group study PRO_ART (Use of Omalizumab Will Increase the Pregnancy Rate, Proof of Concept Study) [124]. Moreover, we addressed all pharmaceutical companies affected by our search for safety and post surveillance data, but the information was only provided for personal, patient-related communication.

A review published on safety and tolerability of omalizumab summarized post-marketing safety data of phase I, II, and III trials and reported 27 exposed pregnancies with 17 reported “normal” deliveries, four elective and six spontaneous abortions [125]. No further information or references of the originating data were provided in this publication. After careful investigation, it was excluded from data analysis.

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Discussion and clinical implications

The safety of biologicals in pregnancy has primarily been reported for the treatment of rheumatological and inflammatory bowel disease patients. Although atopic diseases are among the most common diseases in the reproductive age, investigation, and information on pharmacokinetics, and most importantly, safety is lacking. This EAACI position paper systematically integrates available data by summarizing the current body of evidence on the safety of biologicals during pregnancy in atopic diseases. It intends to reflect the status quo, provide help in counseling pregnant mothers on biologicals, and emphasize the apparent needs of research in this field.

When counseling women diagnosed with asthma on biologicals, it is decisive to emphasize that they are at increased risk for adverse pregnancy outcomes per se.[126] They have an increased risk of preterm delivery, SGA, and LBW infants.[127,128] Appropriate management of difficult-to-treat and severe asthma patients in pregnancy reduce the number of perinatal complications such as preeclampsia. Murphy et al. reported a significantly increased risk of preterm birth, and active management might reduce preterm birth in the asthma population.[126,129] Less is known about the effect of other atopic diseases on pregnancy outcomes. Asthma has been described to pose an increased risk for congenital malformations in children of women without active treatment in one study [129], while others reported a minimally increased risk.[130] [131] It is important to consider that the prevalence of major malformations (e.g., heart defects, neural tube defects, cleft lip) in the general population is 3-5%.[132] Thus, the rate of major congenital malformations (4%) in the 11 above reported omalizumab exposed studies (178 offspring, including 4 twin pregnancies, 7 major congenital malformations) was not higher than expected in a population with severe asthma, atopic disease or chronic urticaria. In the included EXPECT study, 160 infants have been described with the reported 7 major malformations (4.4%) [94]. A very recent comparison of the updated EXPECT pregnancy registry (n=230) with the Quebec External Comparator cohort, a disease-matched asthma population, provided no evidence for an increased prevalence of congenital malformations (8.1% vs. 8.9%), but a higher percentage of preterm births (15% vs. 11.3%) and a lower rate of SGA (9.7% vs. 15.8%)[133] in omalizumab treated mothers. The lower rate in our review of LBW infants might be due to reporting bias of successful pregnancy in case reports and might be underestimated in this systematic review compared to the cited articles above.[127,128] An increased risk of spontaneous abortions was observed in asthmatics, which was

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enhanced in cases of uncontrolled asthma. [131] Similar numbers (8.6%) have been reported for omalizumab in the EXPECT study[94].

As part of this systematic review, all pharmaceutical companies producing biologicals for the treatment of atopic diseases have been contacted to provide safety data. Although the response rate was very high, and data is provided for counseling, they did not allow to publish it referring to the yet too low numbers to draw conclusions. *In vivo* data from animals is not suggestive of enhanced risk. Moreover, pharmacovigilance in case of an adverse event is established (Table 1). Prospective cohort studies of pregnancies exposed to the target medication compared to disease-matched unexposed pregnancies and non-diseased ("healthy") and follow-up of live births have been established (Table 1). Existing national and international severe asthma registries (e.g., European Respiratory Society - Severe Heterogeneous Asthma Research collaboration, Patient-centred (ERS-SHARP) registry[134]) could serve as a source for studies on exposure of pregnant women to biologicals. Furthermore, more academic driven, global networks to investigate the role of biologicals in pregnancy are needed.

In case of unwanted exposure of mothers to biologicals, research has the chance to better understand the impact of certain cytokines on allergy development in the offspring. Given the importance of the first months of life for allergy and asthma development, this information could revolutionize preventive approaches and re-shape our understanding of the mechanisms of allergy development.

So far, few data have been published or accessible from clinical trials about exposure to biologicals during pregnancy in women with atopic disease. Women who are planning a pregnancy or are pregnant are excluded from ongoing trials due to safety concerns, and this leads to the limited available information. There is a risk of publication bias of favorable outcomes in the literature, pregnancy outcome measures such as premterm birth, SGA, LBW, and spontaneous abortions might be underestimated. Thus, preconception counseling, and recommendations on whether to start or continue on biological treatment cannot be provided, and counseling has to be done by the multidisciplinary team. When doing so, the health of the mother and the child has to be taken into consideration before stopping treatment. The benefits and risks need to be outweighed between lack of knowledge and the risk of losing asthma control and thereby jeopardize the maternal and fetal wellbeing. These decisions need to be made on an individual basis and are a prototypic example for informed and shared decision making in medicine (Table 4).

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Drug trial designs suitable for women in the reproductive age are needed. Pragmatic trials would be the perfect match for pregnant women to investigate the outcome and efficacy in a real-world health system practice.[135] Furthermore, due to physiological and pharmacokinetic changes in pregnancy, studies have to be designed to establish recommendations for drug dosing guidelines in pregnancy. [136]

In conclusion, atopic diseases are the most common medical conditions in pregnancy. Biologicals have significantly changed and improved the treatment of these diseases for women in the reproductive age. Nevertheless, we still lack adequate data to reliably counsel women on the maternal and fetal effects of biologicals exposure during pregnancy. Long-term data on immunological changes, risks of infection, and immunosuppression in the child, vaccination recommendations for infants exposed to a biological in utero are not yet available. Good control of atopic disease preconceptionally and during pregnancy is essential to protect the mother and the fetus. Untreated or poorly controlled atopic disease and/or exacerbations during pregnancy put mothers and babies at risk. Most importantly, all women in the reproductive age should be informed by their prescribing physician about potential effects on pregnancy and fertility. Currently, women have to be counseled that the potential risks associated with biological exposure during pregnancy have to be balanced against the risks for themselves and their children caused by untreated atopic disease. Due to the very long half-life of biologicals, preconception counseling by their prescribing physician about potential effects on pregnancy and up-to-date health care provider education is crucial to deliver the best care for mother and fetus.

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Figures

Figure 1: The transfer of biologicals via the placenta and their modes of action in the context of atopic inflammation

Figure 2: The role of cytokine networks in pregnancy

Figure 3: The PRISMA flow diagram for selection of studies on biologicals in pregnancy in atopic diseases

Tables

Table 1: Biochemical and safety data on biologicals approved for the treatment of atopic diseases

Table 2: Characteristics of included studies

Table 3: Summary of findings GRADE working group grades of evidence on biologicals in pregnancy in atopic disease

Table 4: Prescribing and managing biologicals in woman in reproductive age and pregnancy

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Biological	*Target and Antibody type*	*Approved EMA*	*Approved FDA*	*Half-life*	*Animal data*	*Pregnancy data*	*Pregnancy Registry/ TRIAL*
Omalizumab	IgE Humanized IgG1	25/10/2005 Asthma 2014 CSU	20/06/2003 Asthma 2014 CSU	26 days (Asthma)	No adverse effects in animal studies (monkeys)	limited	CLOSED; Xolair Pregnancy Registry ONGOING CLINICAL TRIAL ClinicalTrials.gov Identifier: NCT03727971
Mepolizumab	IL-5 Humanized IgG1/ κ	01/12/2015 Asthma	04/11/2015 Asthma	16-22 days	No adverse effects in animal studies (monkeys)	No published data	Ongoing: The Mepolizumab Pregnancy Exposure Registry: OTIS Vaccines and Medications in Pregnancy Surveillance Study/ VAMPSS
Reslizumab	IL-5 Humanized IgG4	15/08/2016 Asthma	23/03/2016 Asthma	24 days	No adverse effects in animal studies (mice and rabbits)	No published data	
Benralizumab	IL-5 Rα Humanized IgG1/ ϰ	08/01/2018 Asthma	14/11/2017 Asthma	15 days	No adverse effects in animal studies (monkeys), suppression of eosinophil counts in the exposed offspring	No published data from trials, one case report with unknown outcome	Ongoing: Pregnancy Exposure Study ClinicalTrials.gov Identifier: NCT03794999
Dupilumab	IL-4Rα Full human IgG4	20/07/2017 Asthma and atopic dermatitis	28/03/2017 Asthma and atopic dermatitis	unknown	No adverse effects in animal studies (monkeys)	No published data	Ongoing: Pregnancy Exposure Study

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Table 2

	Study (year) Country	Study design	Medical disorder	Biological	Timing of exposure	Pregnancies with known outcome	Live births	Major Anomaly	Minor Anomaly	Small for Gestational Age	Preterm birth in singelton pregnancies	Stillbirth
1	Namazy et al 2014 The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy; USA	Cohort study	Asthma	Omalizumab	188 first trimester, 3 second trimester	169	160/169	7	14	16 / 147	22	1/169
2	Cortese S et al 2013 Omalizumab and pregnancy: A case report; Italy	Case report	Asthma	Omalizumab	First Trimester	1	1	0	N/A	N/A	1	0
3	Hirashima J. et al 2012 A case of an asthma patient receiving omalizumab during pregnancy; Japan	Case report	Asthma	Omalizumab	First Trimester	1	1	0	N/A	1	1	0
4	Kuprys-Lipinska I et al 2014 Omalizumab in pregnant women treated due to severe asthma: two case reports of good outcomes of pregnancies; Poland	Case report	Asthma	Omalizumab	First Trimester	3	2	0	N/A	0	0	0
5	Kuschnir F. et al 2012 Fetal loss in severe asthma and posterior healthy pregnancy and birth with the use of omalizumab case report; Brazil	Case report	Asthma	Omalizumab	First Trimester	1	1	0	N/A	0	0	0
6	Cuervo-Pardo L. et al 2016 Omalizumab use during pregnancy for CIU: a tertiary care experience; USA	Case report	CSU	Omalizumab	First Trimester	4	4	0	N/A	0	0	0
7	Danilycheva I. 2016 Therapy with omalizumab patient with chronic inducible (cholinergic and cold) urticaria and related atopic diseases; Russia	Case report	CSU	Omalizumab	First Trimester	1	1	0	N/A	0	0	0
8	Ghazanfar M. N. et al 2015, Successful and Safe Treatment of Chronic Spontaneous Urticaria with Omalizumab in a Woman during Two Consecutive Pregnancies; Denmark	Case report	CSU	Omalizumab	First Trimester	2	2	0	N/A	0	0	0
9	Gonzalez-Medina M. et al 2017, Omalizumab use during pregnancy for chronic spontaneous urticaria (CSU): report of two cases; Spain	Case report	CSU	Omalizumab	First Trimester	2	2	0	N/A	0	0	0
10	Vieira Dos Santos R. et al 2014, Effects of omalizumab in a patient with three types of chronic urticaria; Brazil	Case report	CSU	Omalizumab	First Trimester	1	1	0	N/A	0	0	0
11	Ensina L.F. 2017, Omalizumab as Third-Line Therapy for Urticaria; Brazil During Pregnancy, Brazil	Case report	CSU	Omalizumab	First Trimester	3	3	0	N/A	0	0	0
12	Ponte P. et al 2010, Apparent safe use of single dose rituximab for recalcitrant atopic dermatitis in the first trimester of a twin pregnancy; Brazil	Case report	Atopic Dermatitis	Rituximab	First Trimester	1	2	0	N/A	0	0	0

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Table 3 GRADE Working Group grades of evidence Biologicals in atopic disease

Patient or population: pregnancy with atopic diseases
Setting: outpatients
Intervention: Omalizumab

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Live births	178/188 (11 observational studies)	⨁◯◯◯ VERY LOW [a]	188 known outcomes, 178 live births are reported incl. 4 twin pregnancies
Still birth	1/188 (11 observational study)	⨁◯◯◯ VERY LOW [b]	One stillbirth was reported in EXPECT out of the 169 known outcomes, which is comparable to rate in asthmatics and the general population
Spontaneous abortion	12/188 (11 observational studies)	⨁◯◯◯ VERY LOW [a,c]	11 have been reported in EXPECT out of 169 reported pregnancy outcomes and one SA was reported in a case report
Preterm birth in delivered singleton pregnancies	24/171 (11 observational studies)	⨁◯◯◯ VERY LOW [a,c]	In EXPECT out of 152 singleton deliveries 22 preterm deliveries were reported and additionally in the 10 case reports two preterm births out of 19 deliveries. The higher rate of preterm birth compared to the general population is known in the asthma population
Small for gestational age	17/148 (11 observational studies)	⨁◯◯◯ VERY LOW [a,c]	Small for gestational age has been reported in 17 infants out of 148 with known birth weight (EXPECT 16/147). The rate of SGA matches the moderate-to-severe asthma population.
Low birth weight	5/126 (11 observational studies)	⨁◯◯◯ VERY LOW [a,c]	4 infants out of 125 known outcomes in EXPECT and one was reported in the case reports. The lower rate might be due to reporting bias of successful pregnancies in the included case report.

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Table 3 GRADE Working Group grades of evidence Biologicals in atopic disease

Patient or population: pregnancy with atopic diseases
Setting: outpatients
Intervention: Omalizumab

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Major congenital malformations	7/178 (11 observational studies)	⨁◯◯◯ VERY LOW [a]	Out of the known 178 live births (incl. 4 twin pregnancies) were 7 major congenital malformations: (cutaneous mastocytosis (1), patent foramen ovale (1), vesicoureteral reflux (1), arteriovenous malformation (1), bilateral renal pelvis dilatation (1), hypospadias (2). This rate was expected in infants born by mothers of moderate-severe asthma population.
Neonatal outcomes	2 (2 observational study)	⨁◯◯◯ VERY LOW [d]	Fetal complications have been only described in two offsprings: One woman was diagnosed with preeclampsia and respiratory failure and her infant with neonatal thrombocytopenia. Another woman was diagnosed with a urinary tract infection and delivered a baby with congenital pneumonia.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Most studies have significant limitations for selection of patients as well as not sufficient description about intervention delivery and outcome assessment. No control group was implemented in any of the studies.
b. The study included is a single arm cohort study, no control group included. Baseline risk between participants was different as the study included pregnant women were exposed to >1 dose of omalizumab within eight weeks before conception or at any time during pregnancy (selection bias). Data collected retrospectively also involve recall bias.
c. Certainty in evidence lowered by publication bias because data was only provided for personal, patient-related communication.
d. It is unclear if patients included in this case reports are the whole cases that investigators have treated with this condition (selection bias).

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Table 4

Biologicals in reproductive age and pregnancy

Aim:

- Preconception counselling by the prescribing physician about potential effects of biologicals on pregnancy and fertility
- Provide state of the art treatment for the mother without harming the fetus

Task: Inform about the balance of benefit versus risk to mother and fetus with limited data

Pregnancy biologicals counselling should include the following aspects

- Information about the impact of the underlying disease on pregnancy outcome
- Information about pregnancy outcomes in the general population such as congenital malformations and miscarriages in the general population
- Inform about the currently available scientific information on specific medication:
  - Potential risks of congenital malformation, miscarriages, preterm delivery, small for gestational age or stillbirth
  - Placental transfer depending on trimester
  - Fetal and maternal monitoring depending on underlying disease and severity

JOINT DECISION:

Together with the women weighing the potential benefits of treated disease and medication versus the potential risks the medication might cause, allows **informed decision making**

The following Information services provide written information and further advice:

ENTIS (European Network of Teratology Information Service (ENTIS) https://www.entis-org.eu/ including services in different languages, English: UK Teratology information service ((UKTIS) https://medicinesinpregnancy.org/Medicine--pregnancy/; German: https://www.embryotox.de/;French: http://www.lecrat.fr/; Dutch: https://www.lareb.nl/

Organization of Teratology Information Specialists https://mothertobaby.org/

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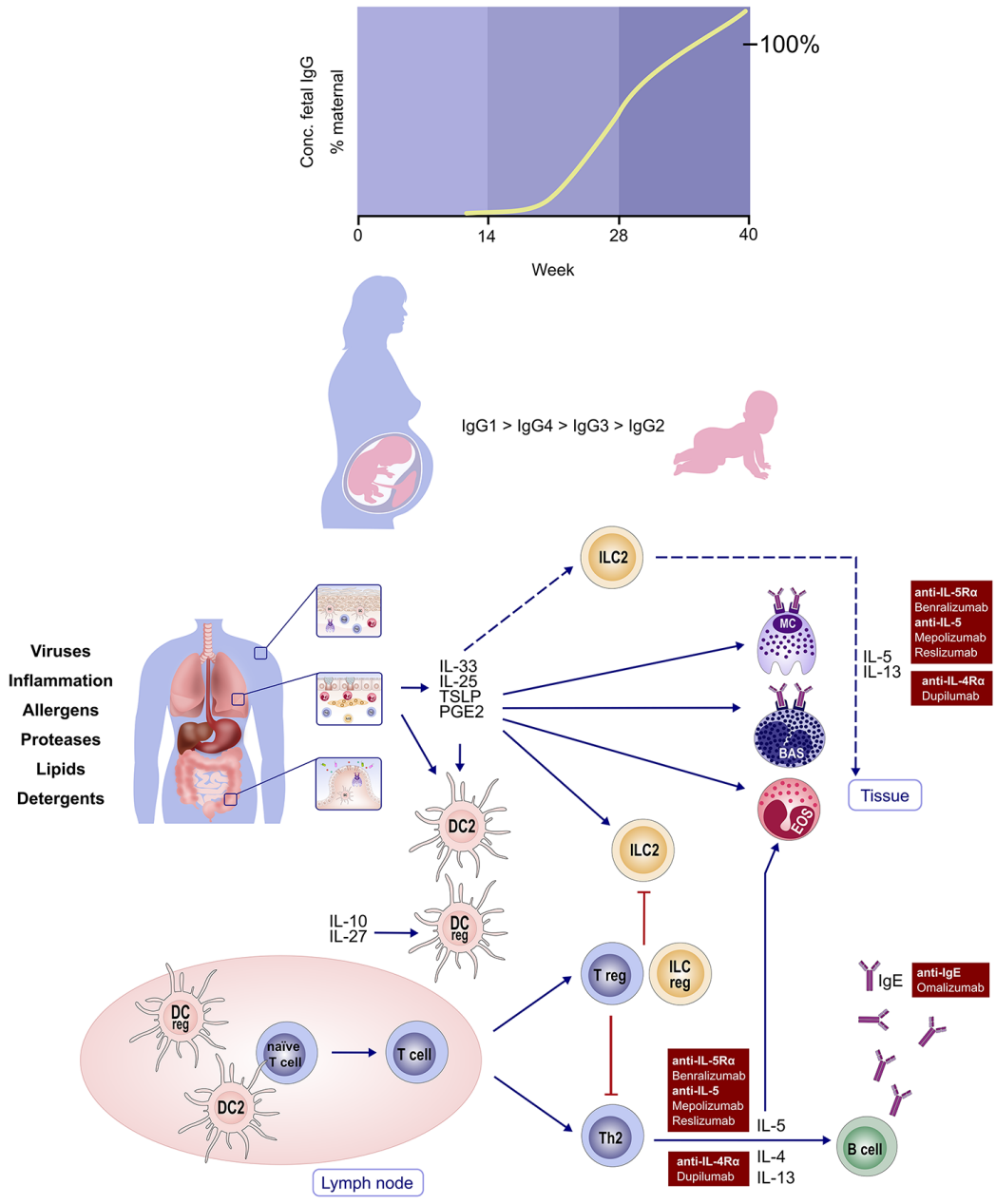


Figure 1

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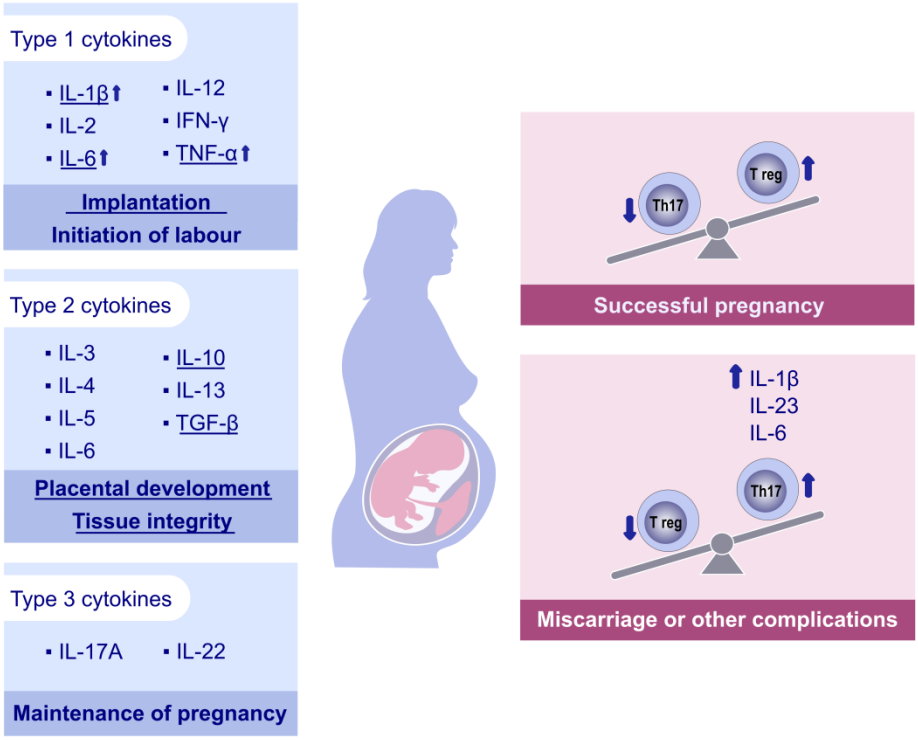
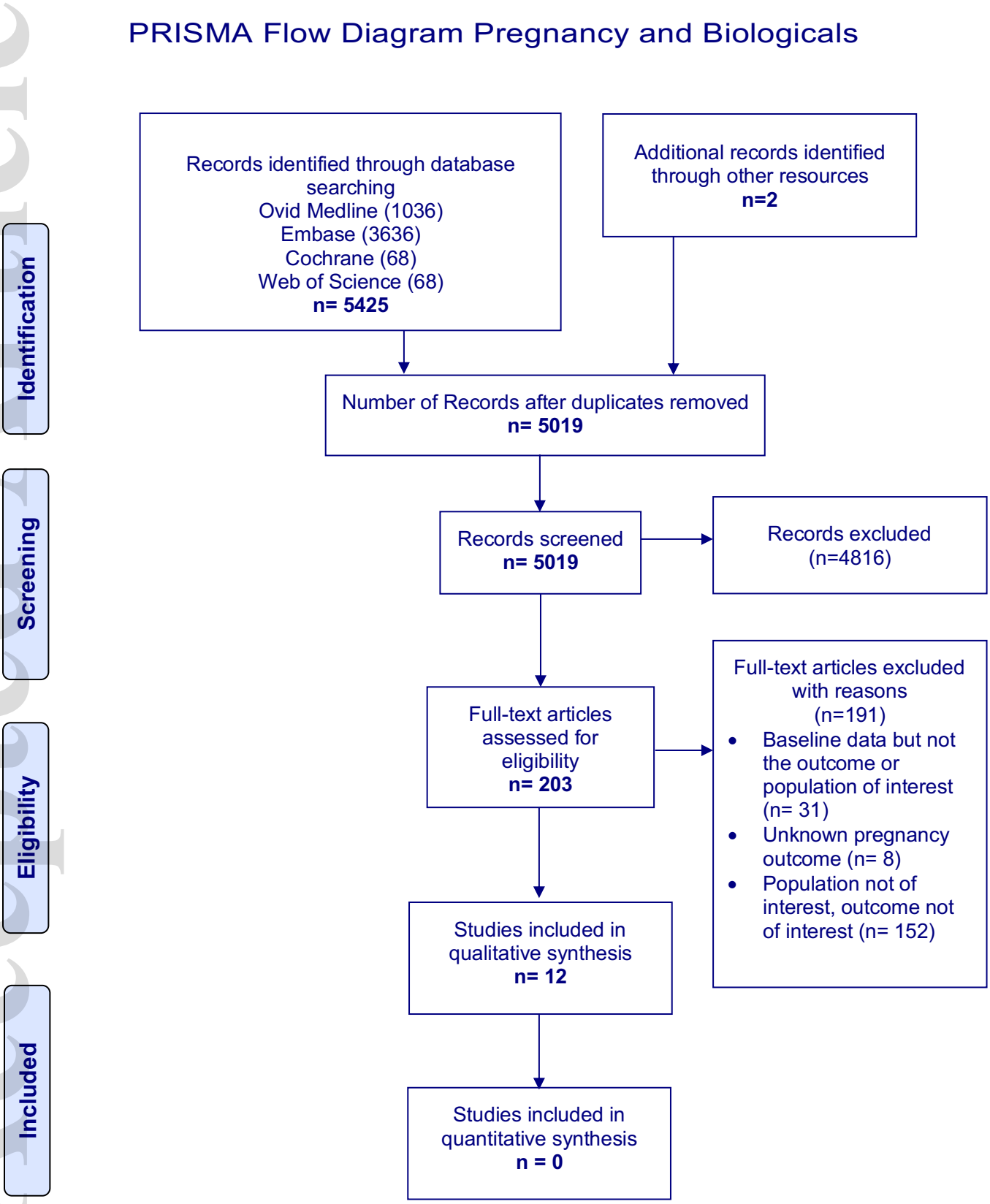


Figure 2

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Figure 3