Title: Belimumab use during pregnancy: A summary of birth defects and pregnancy loss from belimumab clinical trials, a pregnancy registry, and postmarketing reports

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SUPPLEMENTARY INFORMATION

Published literature on SLE

PubMed was used to identify articles with the keywords "systemic lupus erythematosus" AND "pregnancy" AND "fetal loss" published before 30 July, 2019. Referenced studies within reviews and meta-analysis were also examined. Studies were excluded if the definition of foetal loss was not provided, therapeutic/elective abortions were included in the calculation of loss, neonatal deaths were included in the calculation of loss, or the sample size was <20.

A total of 82 previously published studies were identified, of which 44 met the eligibility criteria, where the majority were prospective clinical studies or medical chart reviews. The mean pregnancy loss rate among the 44 studies was 20% (range: 2.9–52.6%). Across the 44 studies, 12 (27.3%) reported disease activity scores (**Supplementary Table 2**). The mean age of female patients in the 12 studies ranged from 26.4 to 42.0, and when reported, the mean SLE duration was 4.3–15.0 years. The Safety of Estrogen in Lupus National Assessment (SELENA)–SLEDAI scores are listed in **Supplementary Table 2.** The pregnancy loss rate in these 12 studies was 2.9–38.5% and positively correlated with SELENA–SLEDAI scores. For instance, a study in which 78% (191/243) patients had a SLEDAI score ≤4, the pregnancy loss rate was 2.9% (95% confidence interval [CI]: 1.3, 5.6), noting the pregnancy loss rate was recalculated to exclude elective terminations.[1] In contrast, a pregnancy loss rate of 38.5% was reported in a different trial in which the 109 participants had a mean (standard deviation [SD]) SLEDAI 2000 score of 10.1 (7.0).[2] Several studies included patients with lupus nephritis or antiphospholipid syndrome in addition to SLE, although currently, most belimumab clinical trials excluded patients with severe renal disease. Most studies defined lupus nephritis as presence of proteinuria >0.5 g/day and/or active urinary sediment with or without an elevation in serum creatinine. As expected, pregnancy loss numbers were generally higher in these studies compared to those that excluded these conditions. For instance, a study conducted between 2000 and 2015 in China, which included a total of 195 pregnancies across 163 patients with SLE and antiphospholipid syndrome reported a pregnancy loss rate of 65.6%.[3] Another study, conducted between 1988 and 2002 in Saudi Arabia, which included 19 pregnancies in 8 patients with lupus nephritis, reported a pregnancy loss rate of 52.6%.[4] As shown in **Supplementary Table 2**, the CIs for pregnancy loss rates were relatively wide; the uncertainty was likely related to low sample sizes (typically N<100).

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Supplementary Table 1 Belimumab clinical trials included within the summary of belimumab use during pregnancy

Study identifier	Study title	Study phase
NCT00712933 (HGS1006-C1074)	A continuation trial for subjects with lupus that completed protocol HGS1006-C1056 or HGS1006-C1057	Phase 3
NCT00071487 (LBSL02)	Safety and efficacy study of lymphoStat-B (belimumab) in subjects with systemic lupus erythematosus (SLE)	Phase 2
NCT00583362 (LBSL99)	A continuation trial for subjects with systemic lupus erythematosus that have completed protocol LBSL02	Phase 2
NCT00410384 (HGS1006-C1056)	A study of belimumab in subjects with systemic lupus erythematosus (BLISS-76)	Phase 3
NCT00724867 (HGS1006-C1066)	A continuation trial for subjects with lupus who completed protocol HGS1006-C1056 in the United States	Phase 3
NCT00424476 (HGS1006-C1057)	A study of belimumab in subjects with systemic lupus erythematosus (SLE) (BLISS-52)	Phase 3
NCT00732940 (HGS1006-C1070)	Phase 2 study of belimumab administered subcutaneously to subjects with systemic lupus erythematosus (SLE)	Phase 2
NCT01345253 (BEL113750)	GSK1550188 A 52 week study of belimumab versus placebo in the treatment of subjects with systemic lupus erythematosus (SLE) located in Northeast Asia	Phase 3
NCT01597622 (BEL114333)	BEL114333, a continuation study of BEL113750 in subjects with systemic lupus erythematosus (SLE) in Northeast Asia, and in Japan subjects completing the open-label extension of HGS1006-C1115	Phase 3
NCT01484496 (HGS1006-C1115)	A study of belimumab administered subcutaneously in subjects with systemic lupus erythematosus (SLE) (BLISS-SC)	Phase 3
NCT01597492 (HGS1006-C1117)	A study to evaluate the effect of belimumab on vaccine responses in subjects with systemic lupus erythematosus (SLE)	Phase 4
NCT01632241 (BEL115471)	Efficacy and safety of belimumab in black race patients with systemic lupus erythematosus (SLE) (EMBRACE)	Phase 4
NCT01639339 (BEL114054)	Efficacy and safety of belimumab plus standard of care in subjects with active lupus nephritis (BLISS-LN)	Phase 3
NCT01649765 (BEL114055)	Pediatric lupus trial of belimumab plus background standard therapy (PLUTO)	Phase 2
NCT01705977 (BEL115467)	Belimumab Assessment of Safety in SLE (BASE)	Phase 4

NCT01894360 (BEL117100)	A study to estimate the relative bioavailability, tolerability and safety of a single dose of belimumab self-administered subcutaneously (SC) by healthy subjects	Phase 1
NCT03312907 (BEL205646)	A study to evaluate the efficacy and safety of belimumab administered in combination with rituximab to adult subjects with systemic lupus erythematosus (SLE) – BLISS-BELIEVE	Phase 3
NCT04136145 (BEL209629)	Single dose study to investigate the pharmacokinetics (PK) and safety of belimumab 200 milligrams (mg) intravenous and 200 mg subcutaneous via auto-injector in Chinese healthy subjects	Phase 1

Supplementary Table 2 Pregnancy loss in patients with SLE in published studies that reported SELENA–SLEDAI scores

Study	Years	Population (region)	N	SELENA/SLEDAI Mean (SD) (or otherwise specified)	Pregnancy loss rate (95% CI)
Deguchi et al. 2018[5] *Clinic-based, prospective study*	2009–2016	Asia	56	Median: 0.0 (range 0–6) Mean 1.14 (1.57) for pregnancy losses (n=7) and 1.35 (1.61) for live births	12.5 (5.6–23.2)
Molad et al. 2005[6] *Prospective case series*	1987–2002	Europe	29	1.8 (3.2)	20.7 (8.8–38.2)
Xu et al. 2015[7] *Retrospective, medical chart review*	2001–2014	Asia	59	2.4 (3.9)	3.4 (0.6–10.8)
Buyon et al. 2015[8] *Longitudinal study*	2003–2012	8 sites in US and 1 in Canada	385	2.8 (3.0)	4.7 (2.9–7.1)
Moroni et al. 2016[9] *Prospective, longitudinal study*	2006–2013	Europe	71	3.4 (4.0)	8.4 (3.5–16.7)
Chen et al. 2018[1] *Retrospective, multicentre study*	2011–2016	Asia	243	78% (n=191) SLEDAI 0–4 18.5% (n=45) SLEDAI 5–9 2.5% (n=6) SLEDAI 10–14 0.4% (n=1) SLEDAI >15	2.9 (1.3–5.6)
Luo et al. 2015[10] *Retrospective, medical chart, cohort study*	1990–2014	Asia	93	Total 3.06 (4.53) Among losses 4.14 (4.71) Among live births 2.73 (4.45)	7.5 (3.3–14.3)
Tandon et al. 2004[11] *Clinic-based, prospective study*	1970–2001	Canada	78	6.1 (4.6)	24.4 (15.8–34.8)
Yan Yuen et al. 2008[12] *Case–control study*	1963–2006	Europe	108	6.7 (0.4)	18.3 (N/A)
Gladman et al. 2010[13] *Clinic-based, prospective study*	1970–2003	Canada	112	7.3 (5.2)	24.1 (16.9–32.7)
Xu et al. 2015[7] *Retrospective, medical chart review*	2001–2014	Asia	18	7.9 (6.2)	22.2 (7.4–45.3)
Sittiwangkul et al. 1999[14] *Retrospective, medical chart review*	1991–1998	Asia	48	8.23 (3.8) to 9.3 (3.05)	20.5 (10.5–34.2)
Ku et al. 2016[2] *Retrospective, medical chart review*	2004–2014	Asia	109	10.1 (7.0)	38.5 (29.7–47.9)
Gladman et al. 2010[13]	1970–2003	Canada	81	10.9 (6.2)	25.9 (17.3–36.3)

Study	Years	Population (region)	N	SELENA/SLEDAI Mean (SD) (or otherwise specified)	Pregnancy loss rate (95% CI)
Clinic-based, prospective study					

CI, confidence interval; N/A, data not available; SD, standard deviation; SELENA–SLEDAI, Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; US, United States.

SUPPLEMENTARY REFERENCES

1. Chen D, Lao M, Zhang J, et al. Fetal and Maternal Outcomes of Planned Pregnancy in Patients with Systemic Lupus Erythematosus: A Retrospective Multicenter Study. *J Immunol Res* 2018;2018:2413637.

2. Ku M, Guo S, Shang W, et al. Pregnancy Outcomes in Chinese Patients with Systemic Lupus Erythematosus (SLE): A Retrospective Study of 109 Pregnancies. *PLoS One* 2016;11:e0159364.

3. Shi H, Teng JL, Sun Y, et al. Clinical characteristics and laboratory findings of 252 Chinese patients with anti-phospholipid syndrome: comparison with Euro-Phospholipid cohort. *Clin Rheumatol* 2017;36:599–608.

4. Rahman FZ, Rahman J, Al-Suleiman SA, et al. Pregnancy outcome in lupus nephropathy. *Arch Gynecol Obstet* 2005;271:222–6.

5. Deguchi M, Maesawa Y, Kubota S, et al. Factors associated with adverse pregnancy outcomes in women with systematic lupus erythematosus. *J Reprod Immunol* 2018;125:39–44.

6. Molad Y, Borkowski T, Monselise A, et al. Maternal and fetal outcome of lupus pregnancy: a prospective study of 29 pregnancies. *Lupus* 2005;14:145–51.

7. Xu X, Liang MY, Wang JL, et al. Clinical features and outcome of pregnancy with SLE-associated thrombocytopenia. *J Matern Fetal Neonatal Med* 2016;29:789–94.

8. Buyon JP, Kim MY, Guerra MM, et al. Predictors of Pregnancy Outcomes in Patients With Lupus: A Cohort Study. *Ann Intern Med* 2015;163:153–63.

9. Moroni G, Doria A, Giglio E, et al. Maternal outcome in pregnant women with lupus nephritis. A prospective multicenter study. *J Autoimmun* 2016;74:194–200.

10. Luo Y, Zhang L, Fei Y, et al. Pregnancy outcome of 126 anti-SSA/Ro-positive patients during the past 24 years--a retrospective cohort study. *Clin Rheumatol* 2015;34:1721–8.

11. Tandon A, Ibañez D, Gladman DD, et al. The effect of pregnancy on lupus nephritis. *Arthritis Rheum* 2004;50:3941–6.

12. Yan Yuen S, Krizova A, Ouimet JM, et al. Pregnancy outcome in systemic lupus erythematosus (SLE) is improving: Results from a case control study and literature review. *Open Rheumatol J* 2008; 2:89–98.

13. Gladman DD, Tandon A, Ibañez D, et al. The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. *J Rheumatol* 2010;37:754–8.

14. Sittiwangkul S, Louthrenoo W, Vithayasai P, et al. Pregnancy outcome in Thai patients with systemic lupus erythematosus. *Asian Pac J Allergy Immunol* 1999;17:77–83.