Psoriasis and adverse pregnancy outcomes: A nationwide case-control study in 491,274 women in Denmark

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Background: The chronic systemic inflammation associated with psoriasis supposedly creates an undesirable milieu for a pregnancy, resulting in an increased risk of adverse pregnancy outcomes (APOs).

Objective: To investigate the association between psoriasis and APOs as well as how the association differs according to psoriasis severity (mild and moderate-to-severe).

Methods: This nationwide register-based case-control study collected data from 1973 to 2017. Cases were APOs (spontaneous abortion, ectopic pregnancy [EP], intrauterine fetal death, and stillbirth). Singleton live births were controls. Adjusted logistic regression models were used for statistical analyses.

Results: In total, 42,041 (8.56%) APOs and 449,233 (91.44%) controls were included. EP was the only APO that was found to be statistically associated with psoriasis (odds ratio, 1.34; 95% CI, 1.06-1.68). Odds ratio for EP was the highest for women with moderate-to-severe psoriasis (odds ratio, 2.77; 95% CI, 1.13-6.76). The absolute risk of EP was 2.48% higher for women with moderate-to-severe psoriasis compared with women without psoriasis (3.98% vs 1.50%).

Limitations: No access to clinical data confirming psoriasis severity.

Conclusion: The present study found a significant association between EP and psoriasis (absolute risk of 3.98%). As EP is the leading cause of maternal morbidity and mortality in the first trimester of pregnancy, our findings call for particular care for women of reproductive age with psoriasis. (JAAD Int 2022;7:146-55.)

Key words: ectopic pregnancy; fetal death; pregnancy; pregnancy outcome; psoriasis; psoriasis severity; spontaneous abortion; stillbirth; women.

INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory disease affecting 2% to 4% of the world's population[1]; approximately half of those are women and most are of childbearing potential, as it has been estimated that 75% of the patients present before the age of 40 years.[2,3] Patients with psoriasis have systemic inflammation driven by T helper type 17 (Th17) cells, and an excess of Th17 cells is known to be associated with adverse pregnancy outcomes (APOs).[4-6] This may affect fecundity (the physiologic potential to bear children) and fertility (the actual

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IRB approval status: Study approval was obtained from the Knowledge Center of Data Protection (reference: VD-2018-533). Approval from an ethics committee is not required for registry studies in Denmark.

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number of children given birth to) and lead to spontaneous abortion, ectopic pregnancy (EP), intrauterine fetal death (IUFD), and stillbirth; of which, EP is the leading cause of maternal morbidity and mortality in the first trimester of pregnancy.[7] Chronic immune-mediated diseases with shared pathophysiologic pathways with psoriasis such as psoriatic arthritis (PsA), rheumatoid arthritis, and inflammatory bowel disease (IBD) have been associated with APOs.[8-10] Furthermore, disease activity in IBD has been reported to be inversely correlated with pregnancy outcomes.[11-13]

Compared with women without psoriasis, women with psoriasis have a higher prevalence of known risk factors[14] for APOs, such as obesity, smoking, gestational hypertension,[15] use of nonsteroidal antiinflammatory drugs, low socioeconomic status, rheumatoid arthritis, IBDs, diabetes, preconception hypertension,[16] thyroid diseases,[17] and lower fertility rates.[18,19]

We hypothesized that psoriasis is associated with APOs. To date, studies regarding psoriasis and APOs have been limited because of either a small sample size or using composite outcomes, mixing pregnancy outcomes with maternal and neonatal outcomes.[18,20] Thus, large nationwide studies are needed with a focus on APOs in women with psoriatic disease.

The objective of the current study was to investigate whether women with psoriasis were at a higher risk of having an APO as well as its association with psoriasis severity and PsA by performing a nationwide register-based case-control study.

CAPSULE SUMMARY

- The chronic systemic inflammation associated with psoriasis may create an undesirable milieu for pregnancy, resulting in an increased risk of adverse outcomes.
- We found a significant association between ectopic pregnancy and psoriasis. Ectopic pregnancy is a rare but potentially life-threatening surgical emergency, warranting attention on women with psoriasis of reproductive potential.

METHODS

Each Danish resident is given a distinctive 10-digit identification number linking that person at the individual level to health care records across registries that have been routinely collected electronically since 1968 for administrative purposes.[21] International Statistical Classification of Diseases and Related Health Problems, Eighth Revision, was used from 1977 to 1993, and International Statistical Classification of Diseases, Tenth Revision (ICD-10), was used thereafter. International Classification of Diseases, Ninth Revision, was never used in Denmark.[22] Study approval was granted by the Danish Health Data Authority (reference: VD-2018-533), with access to data until and including 2017. Ethics approval is not required for register-based research in Denmark.

Study design and population

We conducted a case-control study, in which the study population was identified by collecting the first time (hereafter referred to as the "index date"), in the study period from 1 January, 2004, to 31 December, 2017, a woman had a registered pregnancy outcome. Data regarding the medical and socioeconomic baseline characteristics were collected in the baseline period from 1973 until the individual index date (Fig 1; Supplementary Methods, available via Mendeley at https://doi.org/10.17632/pt3rgg4r6n.1).

Cases were women with an APO, and controls were women with a singleton live birth. Psoriasis was the exposure. This was identified by 1 of the 2 validated methods: either using an ICD-10 code L40.0 or L40.9[23] or using at least 1 redeemed prescription for topical calcipotriol Anatomical Therapeutic Chemical Classification System codes D05AX02 or D05AX52[24] before the index date. As women with PsA also seem to have an increased risk of APO,[15] a subanalysis was performed, in which PsA (ICD-10 M070-73, L40.5) was the exposure.

Psoriasis severity

Psoriasis severity was defined on the basis of psoriasis treatment any time before the index date via hierarchical approach, with moderate-to-severe overruling mild psoriasis.[25] Phototherapy was not used for severity stratification, as it has not been validated to identify patients with psoriasis in the Danish registries. Mild psoriasis[23,24] was defined as the redemption of topical calcipotriol only, ICD-10 for psoriasis only, or both topical calcipotriol and ICD-10 for psoriasis.

Moderate-to-severe psoriasis[26] was defined via administered systemic antipsoriatic drugs: acitretin, cyclosporin, methotrexate, adalimumab, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, secukinumab, and ustekinumab. To substantiate that the treatment was administered for psoriasis, systemic antipsoriatics

Abbreviations used:

APO: adverse pregnancy outcome
EP: ectopic pregnancy
IBD: inflammatory bowel disease
ICD-10: International Statistical Classification of Diseases, Tenth Revision
IUFD: intrauterine fetal death
OR: odds ratio
PsA: psoriatic arthritis
Th17: T helper cell type 17

had to have the indication "treatment of psoriasis" or being administered or dispensed at a dermatology department.

Primary outcomes

APOs were collected from Danish National Patient Registry[27] and Danish Medical Birth Register[28] (access from 1997), identified using ICD-10 codes for spontaneous abortion, EP, and IUFD. Singleton live births and stillbirths were identified from the Danish Medical Birth Register via the date of birth (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/pt3rgg4r6n.1). The details on covariates are provided in the Supplementary Methods.

Statistical analyses

The details on statistical analyses are provided in the Supplementary Methods.

RESULTS

Study population

We identified 491,963 women with first-time (index) pregnancy outcomes during the study period. A total of 689 women with 2 registered outcomes on the same date were excluded. The remaining 491,274 women were included in the study. Of those, 449,233 (91.44%) were live births and 42,041 (8.56%) were APOs: 32,750 (6.67%) spontaneous abortions, 7387 (1.50%) EP, 1228 (0.25%) IUFD, and 676 (0.14%) stillbirths. A total of 6426 (1.31%) women were identified with psoriasis; of those, 6225 (96.87%) women were defined as having mild psoriasis and 201 (3.13%) as having moderate-to-severe psoriasis.

Preexisting and pregnancy-related comorbidities

Women with and without psoriasis had a similar distribution of income and educational level. Women with psoriasis had a higher prevalence of all comorbidities, including pregnancy-related comorbidities; they were more often active smokers throughout pregnancy 846 (13.17%) vs 49,595 (10.23%), had a higher prevalence of prepregnancy obesity 799 (12.43%) vs 48,517 (10.01%), and had a higher use of medications than women without psoriasis (Table I; Supplementary Table II, available via Mendeley at https://doi.org/10.17632/pt3rgg4r6n.1).

Previous pregnancy outcomes and assisted reproductive technologies

Women with moderate-to-severe psoriasis had fewer "1 to 2 previous live births" 24 (11.94%) vs 108, 871 (22.45%), than women without psoriasis. Prevalence of 1 to 2 previous assisted reproductive technology—based treatments was higher in women with psoriasis than in women without psoriasis 383 (5.96%) vs 21,317 (4.40%), and it was the highest in women with moderate-to-severe psoriasis 17 (8.46%) (Supplementary Table II).

APOs and adjusted models

Overall, 32,305 (6.92%) of the women with psoriasis experienced a spontaneous abortion compared with 445 (6.66%) of the women without psoriasis (odds ratio [OR], 1.04; 95% CI, 0.92-1.17) (model 3) (Table II). The risk of EP was significantly higher in all women with psoriasis than that in women without psoriasis (120 (1.87%) vs 7267 (1.50%) (crude OR, 1.25; 95% CI, 1.06-1.50). Significance remained after adjusting for age (model 1) (OR, 1.24; 95% CI, 1.03-1.49); after adjusting for age, body mass index, and smoking (model 2) (OR, 1.35; 95% CI, 1.07-1.70); and in model 3 (OR, 1.34; 95% CI, 1.06-1.68). Post hoc analysis (adjusting for pelvic inflammatory diseases and endometriosis in addition to model 3) did not affect OR for EP (OR, 1.34; 95% CI, 1.06-1.68). Psoriasis was not associated with an increased OR for IUFD or stillbirth.

APOs stratified for psoriasis severity and adjusted models

In women with mild psoriasis, the risk of EP was statistically significant in model 2 (OR, 1.30; 95% CI, 1.03-1.65) and model 3 (OR, 1.29; 95% CI, 1.02-1.64) compared with women without psoriasis (1.48% vs 1.22%). Post hoc analysis did not affect the risk (OR, 1.29; 95% CI, 1.02-1.63). Contrasting, the crude OR of EP was significantly higher in women with moderate-to-severe psoriasis than that in women without psoriasis (OR, 2.77; 95% CI, 1.37-5.64) with nearly 3-fold increase in the risk in model 2 (OR, 2.79; 95% CI, 1.15-6.79) and model 3 (OR, 2.70; 95% CI, 1.11-6.60). Post hoc analysis did not affect the risk (OR, 2.77; 95% CI, 1.13-6.76). The absolute risk difference for EP was 2.48% higher for women with moderate-to-severe psoriasis than that for women without psoriasis (8 EPs (3.98%) vs 7267 EPs

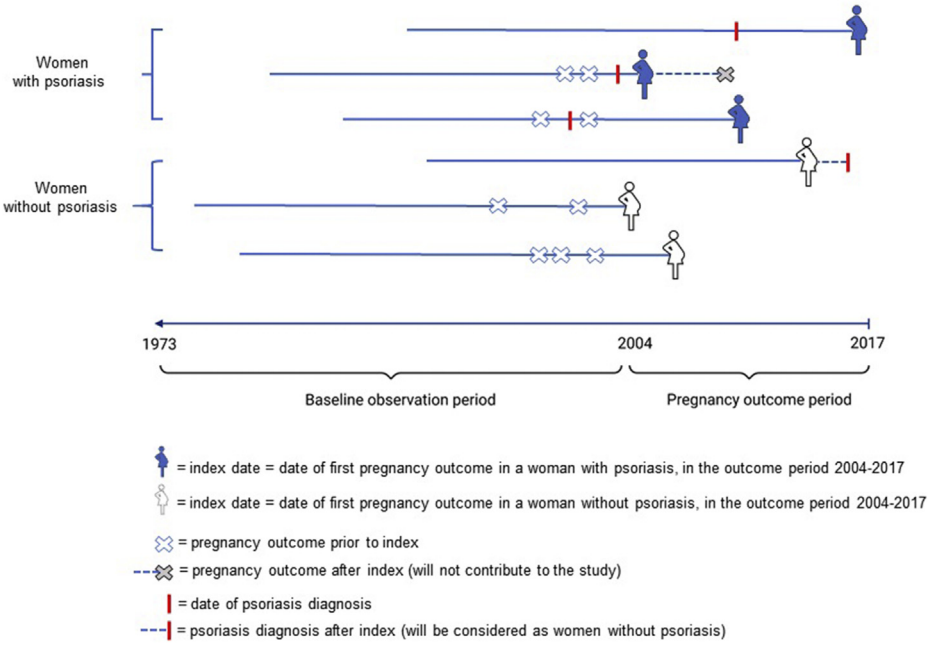

Fig 1. Schematic diagram of the present study's case-control design. Identification and collection of women with and without psoriasis during the entire study period.

(1.50%)). Based on small absolute numbers (<3), women with moderate-to-severe psoriasis had a nonstatistically significant increased risk of IUFD (OR, 2.29; 95% CI, 0.32-16.37) compared with women without psoriasis.

Subanalysis with PsA as the exposure

In total, 291 (0.06%) women had PsA. Of these, 171 (58.76%) women had an overlapping psoriasis diagnosis, of which 127 (43.64%) had mild psoriasis and 44 (15.12%) had moderate-to-severe psoriasis (Supplementary Table III, available via Mendeley at https://doi.org/10.17632/ccznnnzktg.1). Registered APOs were like those of moderate-to-severe psoriasis. Women with PsA had twice the risk of EP (crude OR, 2.12; 95% CI, 1.09-4.13) compared with women without PsA. OR increased in model 2 (OR, 2.48; 95% CI, 1.10-5.58) and model 3 (OR, 2.41; 95% CI, 1.07-5.44). The risk remained after post hoc adjustment (OR, 2.32; 95% CI, 1.03-5.24) (Table III).

DISCUSSION

In this nationwide register-based case-control study, we found that women with psoriasis had an increased risk of EP compared with women without psoriasis. The risk of EP was the highest in women with moderate-to-severe psoriasis and PsA. However, the results from our study did not support the hypothesis that psoriasis is associated with a higher risk of spontaneous abortion, IUFD, and stillbirth.

EP

The prevalence of EP in Denmark is approximately 1%, which corresponds to our findings in women without psoriasis.[29,30] However, the prevalence of EP was higher in all women with psoriasis and the highest among women with moderate-to-severe psoriasis, rendering a nearly 3-fold increased risk of EP, corresponding to an absolute risk of 3.98%.

There could be several potential explanations for the association between psoriatic disease and EP, nonetheless speculative at this point. One explanation could be that women with severe psoriatic disease have a susceptibility to tubal implantation. First, for a pregnancy to be successful, the maternal immune system has to mount a temporary immune tolerance to accept the half foreign embryo via type 2 immunity[31,32] with a shift toward regulatory T cells predominance over Th17 cells. However, in women with chronic inflammatory disorders, Th17 cells can predominate, with reduced number and activity of regulatory T cells.[5] This is also the case in tubal EPs, in which a lower density of regulatory T cells has been found in the uterine decidua than that in an eutopic (normal) pregnancy.[7] Second, studies suggest that classical activated macrophages (M1) are present in abundance in tubal EPs.[7] M1 is induced by the presence of interferon gamma and tumor necrosis factor-alfa. In the fallopian tubes, M1 produces inflammatory cytokines, such as interleukin 6, that inhibit tubal motility and cilia function, and

Table I. Baseline characteristics in women with psoriasis compared with women without psoriasis*

Characteristic	Women without psoriasis		All women with psoriasis		Mild psoriasis		Moderate-to-severe psoriasis	
Total women = 491,274 (100%)	484,848	(98.69)	6426	(1.31)	6225	(1.27)	201	(0.04)
Age at index, y, mean (SD)	30.10	(5.14)	30.40	(5.11)	30.67	(5.10)	30.02	(5.25)
Age at the first registered psoriasis diagnosis, y, mean (SD)			23.64	(6.58)	23.74	(6.57)	20.64	(6.15)
Psoriasis duration at index, y, mean (SD)			7.01	(4.80)	6.93	(4.77)	9.38	(4.91)
Pregnancy-related comorbidities during pregnancy, *n* (%)								
Gestational diabetes	12,553	(2.59)	233	(3.63)	226	(3.63)	7	(3.48)
Preeclampsia	20,525	(4.23)	325	(5.06)	317	(5.09)	8	(3.98)
Gestational hypertension	10,713	(2.21)	170	(2.65)	165	(2.65)	5	(2.49)
Smoking during pregnancy, *n* (%)								
Nonsmoker	385,284	(79.46)	4872	(75.82)	4723	(75.87)	149	(74.13)
Stopped in the first trimester	12,768	(2.63)	223	(3.47)	214	(3.44)	9	(4.48)
Stopped after the first trimester	2572	(0.53)	46	(0.72)	46	(0.74)	0	(0.00)
Active smoker throughout pregnancy	49,595	(10.23)	846	(13.17)	818	(13.14)	28	(13.93)
Smoking status unknown	34,629	(7.14)	439	(6.83)	424	(6.81)	15	(7.46)
Body mass index								
Body mass index, kg/m^2, mean (SD)	23.87	(4.80)	24.41	(5.00)	24.38	(5.00)	25.22	(4.95)
<18.5 (underweight)	24,719	(5.10)	254	(3.95)	250	(4.02)	4	(1.99)
18.5-24.9	294,542	(60.75)	3703	(57.63)	3601	(57.85)	102	(50.75)
25.0-29.9 (overweight)	88,692	(18.29)	1283	(19.97)	1241	(19.94)	42	(20.90)
≥30.0 (obese)	48,517	(10.01)	799	(12.43)	760	(12.21)	39	(19.40)
Unknown	23,889	(4.93)	318	(4.95)	304	(4.88)	14	(6.97)
Administered systemic psoriasis treatment during pregnancy, *n* (%)								
Biologics	42	(0.01)	3	(0.05)	<3		<3	
Cyclosporin	4	(0.00)	<3		<3		0	(0.00)
Redeemed comedication during pregnancy, *n* (%)								
Nonsteroidal antiinflammatory drugs	2151	(0.44)	31	(0.48)	31	(0.50)	0	(0.00)
Methotrexate	6	(0.00)	<3		0	(0.00)	<3	
Acitretin	4	(0.00)	3	(0.05)	<3		<3	
Antidepressants	1314	(0.27)	22	(0.34)	Not shown†		<3	
Age at the first live birth, y, mean (SD)	28.90	(4.85)	29.36	(4.95)	29.37	84.94)	29.01	(5.21)

*Microdata on 1 or 2 individuals are shown as <3 owing to data security requirements.
†Not shown because of referable microdata.

Table II. Stepwise adjustments for odds ratios for adverse pregnancy outcomes (cases) in women with psoriasis (including severity stratification—mild and moderate-to-severe psoriasis) compared with women without psoriasis

Characteristic	Women without psoriasis		All women with psoriasis		Crude*		Model 1†		Model 2‡		Model 3§	
Total women = 491,274 (100%)	484,848	(98.69)	6426	(1.31)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Spontaneous abortion, *n* (%)	32,305	(6.66)	445	(6.92)	1.05	(0.95-1.15)	1.03	(0.93-1.13)	1.02	(0.90-1.16)	1.04	(0.92-1.17)
Ectopic pregnancy, *n* (%)	7267	(1.50)	120	(1.87)	1.25	(1.06-1.50)	1.24	(1.03-1.49)	1.35	(1.07-1.70)	1.34	(1.06-1.68)
Intrauterine fetal death, *n* (%)	1216	(0.25)	12	(0.19)	0.75	(0.42-1.32)	0.74	(0.42-1.31)	0.74	(0.40-1.38)	0.74	(0.40-1.39)
Stillbirth, *n* (%)	666	(0.14)	10	(0.16)	1.14	(0.61-2.13)	1.14	(0.61-2.12)	0.77	(0.34-1.72)	0.76	(0.34-1.70)
Live birth, *n* (%)	443,394	(91.45)	5839	(90.87)								

Characteristic	Women without psoriasis		Mild psoriasis		Crude*		Model 1†		Model 2‡		Model 3§	
	484,848	(98.69)	6225	(1.27)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Spontaneous abortion, *n* (%)	32,305	(6.66)	429	(6.89)	1.04	(0.94-1.15)	1.02	(0.93-1.13)	1.03	(0.92-1.17)	1.05	(0.93-1.18)
Ectopic pregnancy, *n* (%)	7267	(1.50)	112	(1.80)	1.21	(1.00-1.46)	1.19	(0.99-1.44)	1.30	(1.03-1.65)	1.29	(1.02-1.64)
Intrauterine fetal death, *n* (%)	1216	(0.25)	<3		0.71	(0.39-1.28)	0.70	(0.39-1.27)	0.69	(0.36-1.32)	0.69	(0.36-1.33)
Stillbirth, *n* (%)	666	(0.14)	<3		1.16	(0.63-2.20)	1.17	(0.63-2.19)	0.79	(0.36-1.78)	0.78	(0.35-1.76)
Live birth, *n* (%)	443,394	(91.45)	5663	(90.97)								

Characteristic	Women without psoriasis		Moderate-to-severe psoriasis		Crude*		Model 1†		Model 2‡		Model 3§	
	484,848	(98.69)	201	(0.04)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Spontaneous abortion, *n* (%)	32,305	(6.66)	16	(7.96)	1.25	(0.75-2.08)	1.25	(0.75-2.09)	0.78	(0.37-1.66)	0.79	(0.37-1.68)
Ectopic pregnancy, *n* (%)	7267	(1.50)	8	(3.98)	2.77	(1.37-5.64)	2.77	(1.36-5.63)	2.79	(1.15-6.79)	2.70	(1.11-6.60)
Intrauterine fetal death, *n* (%)	1216	(0.25)	<3		2.07	(0.29-14.80)	2.07	(0.30-14.79)	2.29	(0.32-16.38)	2.29	(0.32-16.39)
Stillbirth, *n* (%)	666	(0.14)	0	(0.00)								
Live birth, *n* (%)	443,394	(91.45)	176	(87.56)								

OR, Odds ratio.

*Crude: no adjustment. Microdata on 1 or 2 individuals are shown as <3 owing to data security requirements.

†Model 1: adjustment for age.

‡Model 2: adjustment for age, body mass index, and smoking (nonsmokers as reference).

§Model 3: adjustment for age, body mass index, smoking, income (average income as reference), educational level (short higher education as reference), assisted reproductive technologies, cardiometabolic diseases (preconceptional hypertension, hypercholesterolemia, diabetes, and polycystic ovary syndrome), chronic immune-mediated diseases (rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis), thyroid diseases, combined depression and anxiety, pregnancy-related comorbidities (gestational diabetes, preeclampsia, and gestational hypertension), and exposure to nonsteroidal antiinflammatory drugs. Adjustment for acitretin, biologics, cyclosporin, methotrexate, and antidepressants failed in the analysis because of small numbers; hence, these were removed from model 3. Post hoc analysis (adjustment for pelvic inflammatory diseases and endometriosis) was performed on ectopic pregnancy only.

implantation-promoting tumor necrosis factor-alfa and transforming growth factor-β.

Although embryo implantation and tolerance of pregnancy are extremely complex processes and not yet fully understood, the preexisting inflammatory load in women with severe psoriasis and PsA may facilitate a microenvironment in the fallopian tubes permissive of embryo implantation, resulting in an increased risk of EP. This hypothesis is strengthened by psoriasis' shared immunologic pathway with IBD, which also is associated with an increased risk of EP.[33]

Table III. Stepwise adjustments for odds ratios for adverse pregnancy outcomes (cases) in women with psoriatic arthritis compared with women without psoriatic arthritis

Characteristic	Women without PsA		Women with PsA		Crude*		Model 1†		Model 2‡		Model 3§	
Total women = 491,274 (100%)	490,983	(99.94)	291	(0.06)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Spontaneous abortion, *n* (%)	32,727	(6.67)	23	(7.90)	1.22	(0.80-1.87)	1.19	(0.78-1.82)	1.40	(0.85-2.29)	1.43	(0.87-2.35)
Ectopic pregnancy, *n* (%)	7378	(1.50)	9	(3.09)	2.12	(1.09-4.13)	2.09	(1.07-4.06)	2.48	(1.10-5.58)	2.41	(1.07-5.44)
Intrauterine fetal death, *n* (%)	1227	(0.25)	<3		1.41	(0.20-10.11)	1.40	(0.20-10.00)				
Stillbirth, *n* (%)	676	(0.14)	<3									
Live birth, *n* (%)	448,975	(91.44)	258	(88.66)								

OR, Odds ratio; *PsA*, psoriatic arthritis.

*Crude: no adjustment. Microdata on 1 or 2 individuals are shown as <3 owing to data security requirements.

†Model 1: Adjustment for age.

‡Model 2: Adjustment for age, body mass index, and smoking (nonsmokers as reference).

§Model 3: Adjustment for age, body mass index, smoking, income (average income as reference), educational level (short higher education as reference), assisted reproductive technologies, cardiometabolic diseases (preconceptional hypertension, hypercholesterolemia, diabetes, and polycystic ovary syndrome), chronic immune-mediated diseases (rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis), thyroid diseases, combined depression and anxiety, pregnancy-related comorbidities (gestational diabetes, preeclampsia, and gestational hypertension), and exposure to nonsteroidal antiinflammatory drugs. Adjustment for acitretin, biologics, cyclosporin, methotrexate, and antidepressants failed in the analysis because of small numbers; hence, these were removed from model 3. Post hoc analysis (adjustment for pelvic inflammatory diseases and endometriosis) was performed on ectopic pregnancy only.

Spontaneous abortion, IUFD, and stillbirth

In line with previous studies,[34,35] our study found no increased risk of spontaneous abortion in women with psoriatic disease. However, underreporting of spontaneous abortion has previously been estimated to 25% to 30%.[36,37] In that case, the number of registered spontaneous abortions would be underestimated in our study, expectedly nondifferential misclassification. Despite the high prevalence of known risk factors[38] and as reported by previous studies,[15,39] women with psoriasis and PsA were not at an increased risk of IUFD and stillbirth.

Women with psoriasis and PsA had a higher prevalence of assisted reproductive technology–based treatment in their index pregnancies, indicating a compromised reproduction in either these women or their partner, which is common across chronic immune-mediated diseases with shared disease immunology as that of psoriasis.[40-43]

Systemic antipsoriatic treatment during pregnancy

Considerations about disease fluctuations and compatibility with potential pregnancy must be taken, when choosing optimal psoriasis treatment in women with psoriasis during their reproductive years.[39,44] For example, due to hormonal changes, approximately 15% of the women experience a worsening of their psoriasis during pregnancy.[45]

Furthermore, some systemic psoriasis therapies are contraindicated during pregnancy owing to their teratogenicity (methotrexate and acitretin)[46,47] and others recommended to be used with caution[48] owing to transplacental transfer after the 20th week of gestation (biologics, with the exception of certolizumab pegol) and potential risk of adverse neonatal adverse events[49,50] (Supplementary Table IV, available via Mendeley at https://doi.org/10.17632/ccznnnzktg.1).

In addition, the use of cyclosporin during pregnancy is associated with an increased risk of low birth weight and preterm birth[51,52] and can be problematic to use in psoriatic patients with cardiovascular comorbidity due to the increased risk of hypertension.[53] Therefore, it is reasonable to presume both patient and provider hesitancy toward systemic therapies before and during pregnancy—leaving severe cases with topical and phototherapy only—in which case would bias our findings toward the null.

Finally, we adjusted for drugs associated with an increased risk of APOs (methotrexate,[54] acitretin,[47] nonsteroidal antiinflammatory drugs,[55] and antidepressants[56]), as we adjusted for biologics. However, because of the small numbers, adjustment for acitretin, biologics, cyclosporin, methotrexate, and

antidepressants failed in the analysis and thus were removed from model 3.

Limitations

Important strengths of this case-control study include that data were collected from nationwide registries of high quality, validity, and completeness[21]; thus, typical biases associated with case-controls studies (eg, recall, interview and questionnaire bias) were avoided. Furthermore, we used validated psoriasis definitions[23,24] and psoriasis severity stratification according to the latest consensus.[25] A limitation of our study is that the registries used did not provide information on clinical measurements such as body surface area, psoriasis area severity index to confirm the psoriasis severity at the time of pregnancy, and confounding lifestyle factors such as alcohol and exercise.

Using the previous psoriasis treatment as a proxy for psoriasis severity, as done in the present study, is common practice in epidemiologic studies investigating psoriasis[26,57] and APOs.[15,58,59] Although the use of topical and systemic antipsoriatic treatment has been validated as a method to classify psoriasis severity,[60] it may not apply to a pregnant population. Yet, our study did find that women previously treated with systemic antipsoriatics, defined as having moderate-to-severe psoriasis, had a significantly higher risk of EP (and higher than that in women treated with topical calcipotriol, defined as having mild psoriasis) than women without psoriasis. We speculate that women who have previously been treated with systemic antipsoriatics can produce a systemic inflammatory response, which may characterize immunity more likely of unfavorable implantation. However, clinical studies in pregnant women with psoriasis are needed to validate our assumption that antipsoriatic treatment correlates with the inflammatory state and severity of the disease.

The nature of the epidemiologic method used in the present study, with no access to psoriasis area severity index, body surface area, or blood samples, limits the interpretation of the findings. Causality between psoriasis and EP cannot be concluded but only the significant association. Clinical studies must be conducted to explore the pathophysiologic mechanism of psoriasis inflammation and APOs, to confirm our findings.

CONCLUSION

In this nationwide register-based case-control study exploring the association between psoriasis and APOs, we found that women with psoriasis had an increased risk of EP than women without psoriasis, with an absolute risk 2.48% higher for women defined as having moderate-to-severe psoriasis than that in women without psoriasis (3.98% vs 1.50%). We found no association between psoriasis or PsA and spontaneous abortion, IUFD, and stillbirth. As EP is the leading cause of maternal morbidity and mortality in the first trimester of pregnancy,[7] our findings call for particular care for women of reproductive age with psoriasis, that is, informing sexually active patients to seek emergency gynecologic evaluation in case of lower abdominal pain, unplanned absence of menstruation, and concurrent light vaginal bleeding. Clinical studies are needed to examine the potential causality between psoriasis and APOs.

Conflicts of interest

Dr Johansen has received research funding from the Danish National Psoriasis Foundation and Union Chimique Belge (UCB) and honoraria as consultant and/or speaker from UCB, Galderma, Estee Lauder Companies, and L'Oréal. With no relation to the work reported in this article, Dr Egeberg has received research funding from Pfizer, Eli Lilly, Novartis, AbbVie, Janssen Pharmaceuticals, the Danish National Psoriasis Foundation, the Simon Spies Foundation, and the Kgl Hofbundtmager Aage Bang Foundation and honoraria as consultant and/or speaker from AbbVie, Almirall, LEO Pharma, Samsung Bioepis Co, Ltd, Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, UCB, Mylan, Bristol-Myers Squibb, and Janssen Pharmaceuticals. Dr Jimenez-Solem has received research funding from Eli Lilly, Vertex Pharmaceuticals, and Janssen. Dr Skov has been a paid speaker for AbbVie, Eli Lilly, Novartis, Sanofi, and LEO Pharma; has been a consultant or has served on Advisory Boards with AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma, UCB, Almirall, and Sanofi; has served as an investigator for AbbVie, Sanofi, Janssen Cilag, Boehringer Ingelheim, AstraZeneca, Eli Lilly, Novartis, Pfizer, Regeneron, and LEO Pharma; and has received research and educational grants from Novartis, Sanofi, Janssen Cilag, and LEO Pharma. Dr Thomsen is or recently was a speaker and/or advisor for and/or has received research funding from AbbVie, AstraZeneca, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, Pierre Fabre, Roche, Sanofi, and UCB.

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