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Concise report

Five successful pregnancies with antenatal anakinra exposure

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Abstract

Objectives. Our aim is to add to the limited existing prospective data on IL-1 inhibitor use in pregnancy.

Methods. Data were obtained from the Organization of Teratology Information Specialists Autoimmune Disease in Pregnancy Project, a prospective cohort study of pregnancy outcomes in the USA and Canada. Eligible women were enrolled prior to 19 weeks' gestation between 2004 and 2017. Outcomes were obtained by maternal interview and medical record abstraction.

Results. Five pregnancies with anakinra exposure were identified, all resulting in full-term singleton live births with no major or long-term complications. Three maternal subjects used anakinra for adult-onset Still's disease and two for systemic JIA. For all individuals who discontinued anakinra, some amount of steroid medication was necessary for treatment of disease flare. Two maternal subjects developed oligohydramnios, one also with pregnancy-induced hypertension. Two women had Caesarian sections, one medically indicated and one scheduled. One infant had low birth weight, but follow-up records indicated normal adjusted weight at 1 year. Three women successfully breastfed their infants, at least two of whom continued anakinra while breastfeeding.

Conclusion. Anakinra was used successfully in five full-term pregnancies; however, two subjects developed oligohydramnios, a process that can be linked to fetal renal anomalies. Given previously reported cases of congenital renal anomalies associated with both antenatal anakinra use and maternal hyperthermia, the relationship between maternal IL-1 inhibitor use, uncontrolled maternal febrile disease and fetal outcomes should be further explored.

Key words: pregnancy and rheumatic disease, biological therapies, adult onset Still's, juvenile idiopathic arthritis, autoinflammatory conditions

CLINICAL SCIENCE

Rheumatology key messages

- Successful pregnancies on anakinra can be achieved.
- Anakinra treatment during pregnancy may be associated with less corticosteroid use and better disease control.
- The effect of IL-1 inhibitors and maternal fever on congenital renal anomalies warrants further investigation.

Introduction

Chronic autoimmune and auto-inflammatory conditions often affect young women of childbearing age, posing a dilemma during pregnancy, as these diseases frequently require the use of immune-modulating medications with unknown maternal and fetal consequences. While an increasing amount of data is emerging regarding the safety of more commonly used medications in pregnancy, there is still a dearth of data regarding the safety of anakinra, an IL-1 inhibitor used for febrile conditions such as systemic JIA and adult-onset Still's disease (AOSD), among others. The current recommendation by EULAR is to discontinue this medication prior to pregnancy given the lack of safety evidence [1]. This case series of five successful pregnancies on anakinra serves to add to the limited existing data on IL-1 inhibitor use in pregnancy.

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Methods

Source of the sample

Data were obtained from the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in Pregnancy Project, a prospective cohort study of pregnancy outcomes among women in the USA and Canada. Participants were recruited from pregnant callers to OTIS counselling services throughout the USA and Canada who initiated contact with an OTIS service with questions about any exposure in pregnancy, as well as by direct marketing to consumers through social media and the OTIS MotherToBaby study website. Participants were also recruited through direct marketing to medicine specialists such as rheumatologists, gastroenterologists, dermatologists, neurologists, obstetricians, nurses and other health care professionals through mail, professional meetings and the website. Pregnant women were enrolled in the cohort study between 2004 and 2017, and were considered eligible if they enrolled prior to 19 completed weeks' gestation and had not enrolled in this study with a previous pregnancy. This study was approved by the Institutional Review Board for the OTIS autoimmune diseases in pregnancy study at the University of California, San Diego. All women in the study provided oral consent for participation.

Study design and data collection

Women who consented to participate were interviewed by telephone two to three times during pregnancy using a standard questionnaire about their medical history, prescription and non-prescription medication exposures during pregnancy, history of previous pregnancies, family medical history, pre-pregnancy BMI, and socioeconomic and demographic characteristics of the woman and her partner. Exposure history included start and stop dates of each prescription and over-the-counter medication, as well as indications, dosage changes and frequencies, use of caffeine, dietary supplements, occupational exposures, infections, prenatal testing or other medical procedures and use of recreational drugs, tobacco and alcohol.

Birth outcomes were obtained using a standard interview form completed by telephone shortly after delivery. Women were asked about exposure information through the end of pregnancy, the presence or absence of major structural defects, gestational age at delivery, mode of delivery, length and type of hospital stay, maternal or newborn complications, maternal weight gain, and infant birth weight, length and head circumference.

Medical records from the prenatal care provider, delivery hospital, any specialty providers that managed the woman's care in pregnancy and the paediatrician were collected and data abstracted for additional exposure and outcome information, including validation of maternal self-report of autoimmune disease diagnosis. In addition, the infant's physician was asked to return a form reporting postnatal growth measures and the presence or absence of any major structural defects.

Results

A total of five pregnancies with anakinra exposure were identified. All pregnancies resulted in successful singleton live births. Baseline maternal characteristics for these five pregnancies are outlined in Table 1. The mean maternal age was 30.6 years (range 21.0–36.8 years) with a mean pre-pregnancy BMI of 25.2 kg/m^2 (range 18.4–36.1 kg/m^2). Three maternal subjects used anakinra for AOSD and two used the medication for systemic JIA. One maternal subject was diagnosed with AOSD during pregnancy, and anakinra was started at 20 weeks' gestation. All other subjects had a known diagnosis prior to pregnancy and four subjects used the medication into the third trimester.

All maternal subjects used 100 mg dosing of anakinra, four with daily use and one with weekly use. For each of the five subjects, when anakinra was discontinued, some amount of steroid medication was necessary for treatment. The first subject used anakinra through 20.4 weeks and required methylprednisolone at 22.3 weeks. The second subject, who was diagnosed with AOSD during pregnancy, required prednisone at disease onset (18.6 weeks). The corticosteroid was able to be discontinued at 27.6 weeks, while anakinra was used through 38.1 weeks. The third subject discontinued anakinra at 16.6 weeks and subsequently required high-dose methylprednisolone at 19.1 through 19.7 weeks. Anakinra was restarted from 19.4 to 37.3 weeks' gestation, and the patient did not require any further corticosteroid treatment. The fourth subject discontinued anakinra at 2 weeks' gestation and then required prednisone at 3 weeks. Anakinra was restarted at 9.6 weeks, and corticosteroids were tapered off by 11.7 weeks' gestation. The last subject did not have any steroid use and was continued on anakinra from preconception through the third trimester (Table 1).

As far as additional exposures, the first subject was exposed to LEF 8.8 weeks prior to conception, and given a washout with cholestyramine 6 weeks prior to conception. This patient was also exposed to celecoxib, SSZ and HCQ during her pregnancy, the latter two after discontinuing anakinra at 20.4 weeks. The second subject had additional exposures of duloxetine, tobacco and alcohol. The third subject had a diagnosis of a hypercoagulable state and was continued on anticoagulation with enoxaparin throughout her pregnancy. There were no other significant exposures in the remaining subjects (Table 1).

Maternal and fetal outcomes are outlined in Table 2. All pregnancies were delivered at term with mean gestational age at delivery of 38.9 weeks (range 37.1–40.1 weeks). Two pregnancies had complications: the first subject developed pregnancy-induced hypertension and oligohydramnios, and the fifth subject developed oligohydramnios alone. Two of the five subjects had a Caesarian section, one medically indicated for pregnancy-induced hypertension and low fluid levels, and one previously scheduled. One infant had low birth weight. Postpartum data indicate that this infant had a normal adjusted weight by 4 months of age and through 1 year follow-up. The records for three of the five pregnancies indicate neonatal jaundice, but none was

Table 1 Maternal characteristics for five anakinra-exposed pregnancies: data from the OTIS registry 2004–17

	Maternal age, years	Pre-pregnancy BMI (kg/m^2)	Ethnicity	Obstetric history	Indication for anakinra	Duration of disease	Anakinra timing	Anakinra dosing	Additional medical history	Steroid exposure and timing	Additional exposures
1	30.5	27.6	White/non-Hispanic	G1P0	sJIA	18 years	PC—20.4 weeks	100 mg daily	Asthma	Methylprednisolone 120 mg ×1 at 22.3 weeks	LEF[a] Celecoxib SSZ HCQ
2	30.3	25.0	White/non-Hispanic	G1P0	AOSD	Diagnosed during pregnancy	20.0–38.1 weeks	100 mg daily	NA	Prednisone 60 mg daily 18.6–19.9 weeks; 30 mg daily 20–27.6 weeks	Duloxetine Tobacco Alcohol
3	34.5	36.1	White/non-Hispanic	G3P1	AOSD	4 years	PC—16.6 weeks; 19.4–37.3 weeks	100 mg daily	Prior preeclampsia Hypercoagulable state	Methylprednisolone average dose 62.5 mg daily at 19.1–19.7 weeks	Enoxaparin sodium
4	36.8	18.7	Hispanic	G1P0	AOSD	17 years	PC—2.0 weeks; 9.6–36.7 weeks	100 mg daily	NA	Prednisone taper 30 mg down to 5 mg daily from 3 to 11.7 weeks	NA
5	21.0	18.4	Hispanic	G1P0	sJIA	6 years	PC—37.3 weeks	100 mg weekly	NA	NA	NA

[a]8.8 weeks prior to conception, given washout with cholestyramine 6 weeks prior to conception. sJIA: systemic JIA; AOSD: adult-onset Still's disease; PC: preconception; NA: not applicable.

TABLE 2 Maternal and fetal outcomes for five anakinra-exposed pregnancies: data from OTIS registry 2004–17

	Pregnancy complications	Gestational age at delivery, weeks	Mode of delivery	Birth weight, g	Birth weight, %	Birth length, cm	Birth length, %	Birth head circumference, cm	Birth head circumference, %	Infant sex	Neonatal/ infant complications	Breastfed	Anakinra exposure during breastfeeding	Postnatal weight[a], %
1	PIH, oligohydramnios, breech presentation	37.1	C/S, medically indicated	2419[b]	4	47.0	13	33.0	9	M	Jaundice; right hydrocele; heart murmur, resolved	N	NA	32[c]
2	NA	40.1	NSVD	2940	15	49.0	36	35.0	34	M	Jaundice	Y	Unavailable	14[d]
3	NA	39.3	C/S, scheduled	3632	58	50.2	53	33.0	9	M	Jaundice	Y	Y	44[c]
4	NA	38.7	NSVD	3519	49	52.8	86	33.2	11	M	Tongue-tied	Y	Y	Unavailable
5	Oligohydramnios	39.3	NSVD	2640	7	50.8	72	33.0	14	F	NA	N	NA	Unavailable

[a]Weight determined at longest follow-up date, as specified. [b]Low birth weight. [c]One year follow-up. [d]Four month follow-up. PIH: pregnancy-induced hypertension; C/S: Caesarian section; NSVD: normal spontaneous vaginal delivery; M: male; F: female; Y: yes; N: no; NA: not applicable.

listed as having any major long-term complications or malformations. Three of the five women successfully breastfed their infant with no complications, at least two of whom continued anakinra while breastfeeding (postpartum exposure data were not available for the third subject).

Discussion

Our data from five successful pregnancies suggest that antenatal anakinra use is associated with less corticosteroid use and generally favourable maternal and fetal outcomes. Prior data on anakinra in pregnancy has also been reassuring. Youngstein *et al.* [2] analysed 43 pregnancies retrospectively, 23 of which were maternally exposed to anakinra. One single case of a congenital abnormality was identified (ectopic neurohypophysis with growth hormone deficiency and left renal agenesis) in an AOSD patient with active and refractory disease requiring high-dose corticosteroids. Ten neonates were breastfed by mothers taking anakinra for up to 10 months duration with no serious reported infections, and there were no developmental abnormalities noted in the infants, with a median follow-up time of 18 months.

Another series focused on nine women with cryopyrin-associated periodic syndromes who became pregnant and continued anakinra throughout their pregnancies [3]. In this series, one patient on anakinra was induced for preeclampsia, but otherwise there were no adverse pregnancy outcomes and all infants were born at full term, with the exception of one fetal demise at 30 weeks in a twin dichorionic-diamniotic pregnancy due to renal agenesis. Seven additional cases of antenatal anakinra use in women with AOSD or FMF have been reported in the literature, all resulting in uncomplicated and successful pregnancies [4–7].

Two of the five cases in our study developed oligohydramnios for reasons that are unclear. The first subject in our study with oligohydramnios had exposure throughout her pregnancy to celecoxib, a drug in the NSAID class that has been previously associated with the development of low amniotic fluid levels [8]. This patient also had a history of asthma and exposure to three other DMARDs, thereby complicating her clinical picture. However, given that the only two previously reported congenital abnormalities associated with maternal anakinra exposure are cases of fetal renal agenesis, a process that also may result in oligohydramnios, there is perhaps a potential connection between anakinra and maternal fluid levels that is worth further investigation. Interestingly, maternal fever and 'flu-like illness have also been associated with a higher risk of congenital renal anomalies [9]. Since the diseases that are treated with anakinra tend to be febrile illnesses such as AOSD and systemic JIA, there may be a link between uncontrolled maternal disease and these renal anomalies. Indeed, one of the prior cases of renal agenesis and one of the cases of oligohydramnios in our study were both noted to be in the setting of uncontrolled maternal disease, further supporting this hypothesis.

Anakinra use may have a somewhat protective effect on pregnancy outcomes for individuals with IL-1-driven disease. The miscarriage rate was 30% for pregnancies not on anakinra *vs* 10% for pregnancies on anakinra in the aforementioned cryopyrin-associated periodic syndromes study [3]. An additional study looking at murine models with an elevated IL-1 environment found that when these mice were given IL-1 inhibition, it prevented pregnancy loss [10]. A common theme among prior case exposures is flaring disease activity when taken off anakinra, but good response after the medication is restarted. This pattern of disease activity in relation to the medication, seen in both our study and prior studies, supports the use of the medication during pregnancy, especially when no alternative therapies are available to control disease.

Conclusion

Anakinra was used successfully in five pregnancies from the OTIS registry. All infants were born at full term with no serious complications or adverse outcomes. Pregnancies that discontinued anakinra had some degree of a disease flare requiring steroid therapy, implying that anakinra may be important for controlling disease activity during pregnancy and minimizing corticosteroid use. Two of the five maternal subjects developed oligohydramnios, although additional exposures for one of these pregnancies may have put the patient at elevated risk. However, given two previously reported cases of fetal renal agenesis, a process that also may lead to low fluid levels, as well as reports of maternal hyperthermia being related to congenital renal anomalies, it is worth exploring further a potential link between anakinra, fetal outcomes and maternal febrile disease activity. These data add to the limited knowledge regarding anakinra use in pregnancy and support its use to help achieve successful pregnancies for women who do not have alternative therapies with a larger volume of reassuring safety data at their disposal.

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