



# Obstetric and Gynecological Care in Patients with STAT3-Deficient Hyper IgE Syndrome

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To the Editor,

STAT3-deficient hyper IgE syndrome (AD-HIES; Job's syndrome; STAT3LOF) is a rare primary immune deficiency characterized by elevated serum IgE levels, recurrent skin and lung infections, mucocutaneous candidiasis, and connective tissue, skeletal, and vascular abnormalities [1]. With improved recognition and treatment of infectious complications, affected women are living longer, and gynecologic and obstetric health is becoming increasingly important. Yet, obstetric-gynecologic literature focused on women with primary immune deficiency, including STAT3LOF that is sparse. We describe gynecologic and reproductive health including pregnancy in women with STAT3LOF.

Patients were enrolled with informed consent on an NIAID Institutional Review Board-approved natural history protocol. Retrospective data were obtained by chart review from 50 women aged 18–66 years (median 32.5) with STAT3LOF, of whom 33 were alive. Twenty six had STAT3 mutations in the SH2 domain, 23 in the DNA binding domain, and one in the transactivation (TA) domain. The surviving women completed a structured questionnaire regarding menstruation history; contraception and conception methods; reproductive tract infections/complications; potential barriers to fertility; severity of pulmonary and dermatological manifestations before, during, and after pregnancy; and obstetric complications

and clarified details in follow-up discussions. Denominators varied by information available, such as inability to recall or missing from deceased patients' charts.

Median age of menarche was 12.7 years (range: 10–17.5), similar to the national average of 12.4 years [2]; for most women, menstrual flow and symptoms were comparable with the general population. One woman each reported endometriosis, abnormal uterine bleeding, and uterine fibroids. Four women reached menopause earlier than the US average of 51 years at 38, 40 and 47 years.

During menses, four of 32 women (13%, three with SH2 domain STAT3 mutations, one with a DNA binding mutation) reported worsened pulmonary symptoms, manifesting as increased shortness of breath and sputum; 19 of 38 patients (50%; 10 DNA binding, eight SH2, one TA STAT3 mutations) reported worsened eczema (perineal or other areas), for which half sought medical attention. Anecdotally, one patient with severe perineal eczema flares during menses improved greatly with progestin-releasing intrauterine device (IUD) use.

Current and prior contraceptive use was available for 42 women. Of these, 18 used oral contraceptives (OCPs) with two women stopping for polypharmacy concerns and four others for emotional changes, weight gain, hepatitis, and hematemesis. Condoms were used primarily for 16 women, with four reporting mild contact dermatitis. Ten women used IUDs (nine progestin releasing, one copper) without infectious or other complications. Nine women fearing contraceptive complications or passing on the disease were abstinent. Three patients used plan B (levonorgestrel) as their contraceptive method. Two patients used diaphragm/spermicide, depot-medroxyprogesterone, and vaginal rings. Seven women underwent surgical sterilization by tubal ligation or hysterectomy.

Gynecological infections were common. Thirty of 42 women reporting (71%) had frequently recurrent perineal or breast abscesses, including 19 women with breast, 15 with labio-perineal, and 5 with vaginal abscesses; 17 (40%) required incision and drainage and oral antibiotics. Abscesses

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were seen more commonly in women with SH2 domain STAT3 mutations ( $n = 21$ ) than those with DNA binding mutations ( $n = 9$ ) ( $p < 0.01$ ; Chi-square analysis). Culture data were not available for many of the infections; however, *Staphylococcus aureus* and/or *Enterococcus* species were isolated in at least five cases. Vaginal candidiasis was reported by 31 of 35 women, most requiring chronic antifungal suppression. Non-candida vaginitis and bacterial vaginosis were reported by six women.

Gynecological surgeries were uncomplicated with four women undergoing tubal ligation, two hysteroscopies (fertility, fibroid removal), and two hysterectomies (fibroids; post-Caesarian (C-)section). Four underwent dilatation and curettage, one for hydatidiform mole, and others for miscarriage/abortion. One patient with severe dyspareunia underwent introital nerve ablation.

Twenty-three of 33 women (70%) with available records had pap smears. Of 16/23 (70%) reporting abnormal pap, two had heavy yeast and four underwent HPV laser ablation, LEEP (loop electrosurgical excision procedure), or cryotherapy. No cervical cancer was identified. Of 13 women reporting mammography, seven over age 40 years had cancer screening, and six others had suspicious nodules or infections. Lumpectomy confirmed fibroadenomas in three patients, abscess in two, and atypical ductal hyperplasia/fibrocystic changes in one. Generally, breast abscesses, discussed above, were detected and monitored through ultrasound or other imaging. One woman had breast reduction surgery.

Over 30% of our cohort chose not to conceive to avoid having affected offspring or exacerbating underlying disease. Difficulty conceiving was reported in one patient with polycystic ovarian syndrome, who conceived with clomiphene. Sixteen women reported 39 pregnancies, with the first pregnancy at 14–33 years (median 29). Six of 16 (38%) women reported miscarriages, with three (19%) reporting multiple miscarriages, higher than 1% for the general population [3]. Miscarriages were evenly distributed between women with SH2 domain mutations and DNA binding mutations.

Pregnancy complications included worsened eczema in two women and worsened pulmonary disease with infection in three that continued postpartum. Five babies were born prematurely, two before 33-week gestation (premature labor, chorioamnionitis) and three between 33 and 36 weeks. Three of these women had mutations in the DNA binding domain and two in the SH2 domain. No patient reported gestational hypertension, diabetes, vaginal bleeding, or other placental abnormalities.

Of the 27 live births occurring in 15 women, four were C-section and two resulting in wound infection and poor wound healing. One patient underwent hysterectomy 2 weeks post-C-section for unremitting uterine hemorrhage, and another underwent endometrial ablation for prolonged postpartum bleeding. Two women with significant postpartum breast

candida infection experienced resolution after discontinuing breastfeeding.

With earlier recognition and diagnosis, and improved antimicrobials, women with primary immunodeficiencies including STAT3LOF are surviving well into adulthood; thus, optimizing gynecologic and obstetric health is essential. We report on the systematic medical record review of adult women in our cohort to provide clinical observations and enable better counseling around issues such as birth control and pregnancy.

A few important messages emerged (Table 1). First, as was recently described in the French cohort, gynecological infections are common and can be severe [4]. Many women had breast and perineal abscesses, which were frequently recurrent or chronic and likely under-recognized. Women merit screening for these infections with gynecologic consultation for potential abscess drainage. We found the infections to be more common in women with STAT3 mutations in the SH2 domain; prior genotype/phenotype differences have not been seen for infection occurrence, and this requires further consideration with increased cohort sizes of STAT3LOF patients.

Second, the choice of contraception is important as there can be interactions between oral contraceptives and systemic antimicrobials, such as with triazole antifungals. Additionally, the increased risk of thromboembolic events with oral contraceptives warrants consideration especially given the increased incidence of middle-sized artery vasculopathy with STAT3LOF, resulting in thrombosis of coronary artery aneurysm and myocardial infarction [5]. Our cohort has used mainly progestin-releasing IUDs, that were well-tolerated, without upper reproductive tract infections, mitigated concern of polypharmacy, and lightened menses improving menses-related eczema in at least one woman.

Next, with improved health and improved outcomes in children with early diagnosis, more women may choose to conceive. We noted an increased risk of miscarriage, which may relate to STAT3's role in interacting with progesterone receptor to enable successful implantation. Mice with *stat3* conditionally ablated in the uterus were unable to conceive [6]. Although most pregnancies were uncomplicated except for several premature deliveries, which was also seen in a report of pregnancies in CVID [7], two patients experienced significantly worsened lung disease with parenchymal destruction. The pulmonary infection symptoms in this disease are often mild, and there is a reluctance to aggressively diagnose infections using chest imaging in pregnant women. Some antimicrobial prophylactic regimens are contraindicated during pregnancy, such as trimethoprim/sulfamethoxazole and azoles (for chronic use during the first trimester). Other prophylactic antibiotics, such as azithromycin and beta lactams (e.g., cephazolin), may be considered. In addition, topical antiseptics, such as chlorhexidine, can be used to diminish the *Staphylococcus aureus* skin colonization. For

**Table 1** Clinical features

|                       | Clinical features in cohort  |
|-----------------------|--|
| Menses                | Some report flares of eczema (50%) and respiratory (13%) symptoms; early menopause for several                       |
| Contraception         | Drug interaction concern with OCPs; 10 with IUDs without complications   |
| Breast infections     | 45% of women report breast abscess, frequently requiring drainage  |
| Perineal infections   | 48% reporting perineal abscess, frequently requiring drainage  |
| Gynecologic surgeries | Hysterectomy, hysteroscopy, tubal ligations without complications  |
| Miscarriages          | 38% of women reported miscarriage, with recurrent miscarriage reported by 20%  |
| Pregnancy outcomes    | 15 women with 27 live births. Complications included prematurity (five), eczema flares, and lung disease progression |
| Malignancy            | C-section infections and one postpartum hemorrhage leading to hysterectomy<br>No breast or cervical cancer noted     |

mucocutaneous *Candida* infections, topical therapies (such as nystatin and azoles) can be used to control infections. Clinicians should obtain sputum cultures and treat possible infections aggressively to prevent lung parenchyma destruction. In addition, postpartum bleeding leading to intervention, including one emergency hysterectomy, may relate to vascular anomalies in these patients. Another report described a woman with STAT3LOF requiring surgery 2 days post-C-section for a large hematoma removal [8]. Finally, the occurrence of chorioamnionitis and of wound infections after C-section suggests considering extending prophylactic antibiotics and instituting evidence-based interventions to decrease risk of complications.

As survival improves for women with STAT3 deficiency, it is important that routine gynecological health concerns are not neglected. Several women had not undergone routine cervical cancer screening. We do not know whether having a STAT3LOF mutation confers protection against developing breast cancer or other cancers associated with increased STAT3 signaling. Monitoring obstetric and gynecologic outcomes and complications will allow us to better counsel these women.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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