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ORIGINAL ARTICLE

High prevalence of ovarian cysts in premenopausal women receiving sirolimus and tacrolimus after clinical islet transplantation

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Summary

We encountered an unexpectedly high rate of ovarian cysts in premenopausal women receiving sirolimus and tacrolimus following islet transplantation. The goal of this retrospective chart review was to determine the frequency of ovarian cysts found on pelvic ultrasound examinations of female islet transplant recipients and to look for potential causal factors. Fifty-seven women with a median age of 42.5 years underwent islet transplantation at the University of Alberta. Ovarian cysts were found in 31 out of 44 (70.5%) premenopausal and two out of 13 (15.4%) postmenopausal women ($P = 0.001$). No women using combined oral contraception developed ovarian cysts. Eight women required surgery; in four women undergoing cystectomy or unilateral oophorectomy, ovarian cysts recurred. Sirolimus withdrawal was associated with a reduction in cyst size and resolution of cysts in 80% of subjects. The risk of ovarian cysts should be discussed with female islet transplant candidates and pelvic ultrasounds performed routinely post-transplant.

Introduction

The benefits of islet transplantation in selected type 1 diabetes patients must be balanced against the risks of life-long immunosuppression [1]. We have observed an unexpectedly high prevalence of ovarian cysts in women undergoing clinical islet transplantation (CIT) and receiving sirolimus and tacrolimus for immunosuppression. Ovarian cysts have been reported in approximately 7% of premenopausal women [2] and ranging from 3% to 18% in postmenopausal women [3] in the general female population. Also, ovarian cysts are not common (1–7%) following renal transplantation [4,5]. Conversely, a recent small series from the University of Miami reported finding ovarian cysts in eight out of 13 (61%) female islet transplant recipients [6].

The underlying mechanism for ovarian cyst formation in islet transplant recipients is not clear. Neither is the natural history nor the relationship with immunosuppression. We therefore sought to examine the incidence, progression and response to therapy of ovarian cysts in a retrospective analysis of pelvic scans performed in 57 female islet transplant recipients undergoing transplantation at the University of Alberta between March 1999 and July 2007.

Patients and methods

Transplants were performed as previously described in C-peptide negative type I diabetic subjects with frequent and severe hypoglycemia with hypoglycemia unawareness and/or glycemic lability [7]. Standard maintenance

immunosuppression was with sirolimus (trough levels 12–15 ng/ml for the first 3 months then 7–10 ng/ml thereafter) and tacrolimus (target trough level 3–6 ng/ml). A small group of patients received tacrolimus at higher doses (target trough levels 10 ng/ml) along with mycophenolate mofetil (1 g b.i.d. as tolerated) for immunosuppression from the time of transplant.

Routine abdominal ultrasound scans were scheduled pretransplant, postoperative day 1, day 7, and 1 month post-transplant; and annually thereafter as routine clinical care. Additional pelvic ultrasound scans were performed as deemed clinically necessary when ovarian cysts were detected. Reports of all pelvic imaging studies (ultrasound, CT or MRI) were reviewed and included in this study. Ovarian cysts of >2.5 cm in diameter were deemed clinically significant. Complete resolution was defined as a decrease in cyst size to <2.5 cm in diameter. Partial resolution was defined as a >50% decrease in cyst size but where cyst diameter remained >2.5 cm. Cysts with diameter >2.5 cm which did not decrease in size by more than 50% were deemed to be persistent. When multiple cysts were present (concurrently or over time), the maximal diameter of the largest cyst was used in the analysis.

All clinical data were extracted from patient charts. Menopausal status and menstrual history were also determined by chart review. Menstrual abnormalities were defined as any change from pretransplant status (including oligomenorrhea or menorrhagia) and menopause as complete cessation of periods for >12 months with or without menopausal symptoms. The study was approved by the University of Alberta Health Research Ethics Board.

Data are presented as the mean ± standard error or median (25th to 75th percentile). Univariate analysis was performed using chi-squared test, Fisher's exact test or Mann–Whitney *U*-test using SPSS 15.0 for Windows (SPSS Incorporated, Chicago, IL, USA). Statistical significance was set at 5%.

Results

The characteristics of the 57 subjects are presented in Table 1. Forty-four subjects were premenopausal and 13 postmenopausal at the time of CIT. The median duration of follow-up from first transplant was 53.1 (32.0–70.4) months.

All 57 subjects had pretransplant imaging, but in 32 subjects pelvic visualization was inadequate or unreported. Pre-existing ovarian cysts were reported in six out of 25 (24%) subjects. Post-transplant, two subjects had no further cysts while new cysts developed in the other four.

Table 1. Baseline characteristics of female CIT recipients.

	Female patients (n = 57)
Age at first transplant (years)	42.5 (36.1–49.4)
Diabetes duration (years)	28.8 (18.8–36.5)
Follow-up duration (months)	53 (32–70)
Menopausal status at transplant	
Premenopausal	44 (77.2%)
Postmenopausal	13 (22.8%)
Pretransplant insulin requirement (μ/kg/day)	0.55 (0.48–0.72)
Pretransplant body mass index (kg/m^2)	23.4 (22.0–25.0)
Pretransplant HbA_{1c} (%)	8.0 (7.0–9.6)

Data are median (25th–75th percentiles) or number (%).

New ovarian cysts were detected in 33 out of 57 patients (57.9%) at a median of 235 (119–405) days after the first CIT. The duration of post-transplant follow-up was similar in subjects with or without ovarian cysts (59 vs. 36 months respectively, $P = 0.07$). The median maximal cyst diameter was 6.0 (3.8–7.6) cm. Thirteen (39.3%) women only had unilateral cyst(s), while the remaining women had bilateral cysts (either concurrently or during the observation period). Most cysts were asymptomatic and noted incidentally on routine imaging. However, 14 subjects (42.4%) reported pelvic pain. In four cases, severe pelvic pain resulted in emergency room visits because of ovarian cyst rupture ($n = 2$) or torsion ($n = 2$).

Cysts occurred more frequently in premenopausal than postmenopausal subjects [31/44 (70.5%) vs. 2/13 (15.4%), $P = 0.001$]. Among premenopausal subjects, menstrual abnormalities were significantly more likely in women with ovarian cysts than in those without [26/33 (78.8%) vs. 7/24 (29.2%), $P < 0.001$]. Premenopausal women taking estrogen and/or progesterone, e.g. combined oral contraceptive (COC), were much less likely to develop cysts (0/7 vs. 31/37, $P < 0.001$). However, the use of hormonal therapy after cyst development did not affect cyst outcome (data not shown). The use of gonadotrophin releasing hormone (GnRH) analog for 3 months in one subject was associated with partial cyst resolution (decreased from 15 to 3.5 cm) but recurrence (6.7 cm diameter) after GnRH withdrawal.

Eight subjects had surgical procedures because of pelvic pain unresponsive to medical or conservative measures. In four cases, bilateral oophorectomy was performed. In all four subjects undergoing ovarian cystectomy or unilateral oophorectomy, there was recurrence of cysts. Histology was benign in all cases.

Ovarian cysts occurred more frequently in subjects taking sirolimus plus tacrolimus than those taking tacrolimus plus mycophenolate mofetil [33/53 (62.3%) vs. 0/4 (0%), $P = 0.027$]. Three of the four women taking

tacrolimus plus mycophenolate mofetil were postmenopausal at the time of islet transplantation. Among women taking sirolimus, average sirolimus trough levels were similar between those who developed ovarian cysts and those who did not [12.1 (10.9–13.3) vs. 12.2 (11.5–12.6) ng/ml, $P = 0.993$]. Sirolimus was discontinued for various reasons in 26 out of 33 women with ovarian cysts, including in nine patients for ovarian cysts. Cysts were larger in subjects whose sirolimus was discontinued compared with subjects continuing sirolimus [6.2 (5.4–8.0) vs. 4.1 (3.4–6.2) cm, $P = 0.024$]. The proportion with partial or complete cyst resolution was similar in those who did or did not discontinue sirolimus [12/15 (80%) vs. 6/8 (75%), P = NS].

Discussion

It is clear that ovarian cysts are a common complication (70%) in premenopausal women undergoing CIT and receiving the combination of sirolimus and tacrolimus for maintenance immunosuppression. This rate is substantially higher than that seen in either the general female population (3–18%) [2,3] or renal transplant recipients (1–7%) [4,5].

A causal role for sirolimus is suggested as women who did not receive sirolimus did not develop cysts and its discontinuation was associated with a reduction in cyst size, while recurrence was the norm in cysts treated surgically. The larger cyst size in women who had discontinued sirolimus likely reflects the fact that large or symptomatic cysts were an indication for stopping the drug. It is striking that use of the COC seems to protect from cyst development.

During a normal menstrual cycle ovarian follicles grow in response to follicle stimulating hormone (FSH) and a single dominant follicle enlarges between days 9 and 14. Ovulation is triggered by a surge of luteinizing hormone (LH), which stimulates progesterone and prostaglandin synthesis. Progesterone enhances plasminogen activator activity, which together with prostaglandin causes digestion and rupture of the follicular wall [8]. Ovarian cysts can develop from a follicle or the corpus luteum and are usually <2.5 cm in diameter, but large cysts can be seen rarely in otherwise normal women [3].

The anti-proliferative effect of sirolimus [9,10] might interfere with the digestion and rupture of the follicular wall and result in large cysts. A previous report of ovarian cysts after CIT found very low progesterone levels, which is consistent with the presence of unruptured follicles [6].

The suggestion that these ovarian cysts are because of sirolimus preventing rupture of normal cysts is supported by our finding that cysts were rare in postmenopausal women and women whose LH and FSH (and therefore follicle development and ovulation) were suppressed by COC. This might also explain the relatively high rate of ovarian cysts after CIT compared with other solid organ transplant settings where most recipients are anovulatory prior to and for some time after transplantation [11–13]. In contrast, most islet transplant recipients have had normal menses (and presumably normal ovulation) prior to transplant.

Another unique factor in CIT is the avoidance of glucocorticoids. It is possible that glucocorticoids may be protective against the development of ovarian cysts by its anti-proliferative effects and by suppressing adrenal androgen production. This could further explain the low prevalence of ovarian cysts following solid organ transplants.

The longer duration of follow-up in women who developed ovarian cysts (while not reaching statistical significance) suggests that the risk of developing cysts increased with increasing exposure to immunosuppression.

Like any uncontrolled retrospective analysis our study has several limitations. We did not systematically examine the hormonal profile of all subjects which might clarify the pathophysiology of the cysts. As pretransplant pelvic imaging was either limited or not reported in 32 subjects we cannot exclude the possibility that some ovarian cysts may have been pre-existing. Furthermore, subjects with cysts were more likely to have repeat imaging, thus potentially detected physiological cysts that were asymptomatic. Nevertheless, it seems unlikely that the very high prevalence of ovarian cysts is artifactual.

These data suggest that the risk of ovarian cysts and menstrual disturbances should be discussed with all female islet transplant candidates. It would seem prudent to perform baseline pelvic ultrasound scans pretransplant and to repeat these on a regular (annual) basis post-transplant, or if symptoms of pelvic pain are noted. For larger, persistent or symptomatic cysts, alternate immunosuppression regimens could be considered. Avoidance of the long-term use of sirolimus may also be considered as there are myriad other adverse effects associated with it, reviewed recently in Ref. [14]. It may be reasonable to suggest COC for premenopausal islet transplant candidates, both to prevent pregnancy and potentially to reduce the risk of developing ovarian cysts. Further studies are required to determine the underlying cause for the high prevalence of ovarian cysts observed after CIT and to determine whether COC can reduce the risk of developing this complication.

Authorship

EA, AK, WA and PAS: analyzed data, wrote paper. RB and TA: analyzed imaging data, reviewed paper. CMD,

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EAR and AMJS: designed and performed study, reviewed paper.

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