
Scintigraphic Localization of Ovarian Dysfunction

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To assess the potential role of scintigraphy in the evaluation of clinically and biochemically suspect ovarian hyperandrogenism (HA), dexamethasone suppression ^{131}I -6 β -iodomethyl-19-norcholesterol (NP-59) scans were performed to characterize ovarian function in nine patients. Pelvic ultrasound and/or computed tomography (CT) identified anatomic abnormalities in the adnexal region in six women in whom there was discernible pelvic accumulation(s) of NP-59. In the remaining three patients testosterone levels were normal or only slightly elevated and the NP-59 scan did not demonstrate abnormal adrenal or pelvic uptake. CT and/or ultrasound studies failed to demonstrate an abnormality in the pelvis suggesting excessive peripheral conversion or abnormal end organ sensitivity of androgen precursors as potential etiologies of their HA. In three women with androgen secreting lipid tumors of the ovary, unilateral, pelvic NP-59 activity was noted; these tumors were subsequently resected. Two women with bilateral pelvic NP-59 uptake were later shown to have hyperthecosis with markedly asymmetric and enlarged ovaries. In one woman the extent of asymmetric NP-59 uptake was anticipated by the asymmetry of ovarian vein androgen levels at selective venous catheterization. In another woman with markedly asymmetric polycystic ovary disease, intense focal uptake of NP-59 localized to the side of the anatomically abnormal, enlarged ovary. Thus, our preliminary study reviews our experience to date and suggests that NP-59 scintigraphy may be used to localize both tumorous and nontumorous ovarian dysfunction in states of HA and virilization.

J Nucl Med 29:1644-1650, 1988

Hirsutism is often a manifestation of androgen excess and may be a result of a variety of pathologic processes as well as familial or ethnic traits (1). The diagnosis is usually reached after the integration of data obtained by physical examination, and hormone measurements in serum and urine (androgen profile). Effective treatment depends upon identifying the source(s) of androgen hypersecretion (HA) (2-3). Despite complete hormonal evaluation, including suppression and stimulation studies of plasma and urinary androgens, their precursors and secretagogues, there are cases in which distinguishing potential site(s) of excessive androgen secretion is problematic. In these cases it is difficult to ascertain whether the etiology of HA is adrenal and/

or ovarian, the result of excessive peripheral androgen precursor conversion, or abnormal end organ sensitivity (4).

Studies of anatomic localization to identify the source(s) of androgen excess have repeatedly confirmed this multiplicity of etiologies of androgen production that confound attempts at localization with ultrasound or high resolution computed tomography (CT), and make selective venous hormone sampling necessary (5, 6). Functional scintigraphic imaging has been previously shown to identify the adrenal contribution to circulating androgens in women with HA where tumorous and nontumorous adrenal dysfunction has been depicted by iodine-131-6 β -iodomethyl-norcholesterol (NP-59) (7-9). Numerous anecdotal reports have suggested the ability of NP-59 scintigraphy to visualize tumorous ovarian dysfunction in HA and this approach was used in the present study to review our experience in the scintigraphic evaluation of women with suspected ovarian androgen excess (5).

Received Oct. 6, 1987; revision accepted Mar. 28, 1988.

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METHODS

Nine women with clinically suspect ovarian HA were studied with NP-59 scintigraphy. Each patient was imaged after history, physical examination, and biochemical studies including measurements of urinary 17-ketosteroids, serum testosterone, and dehydroepiandrosterone sulfate (DHEAS) levels and, in most cases, the response of testosterone and DHEAS to dexamethasone suppression (8). When performed, CT (GE Models 8800 and 9800) scans of the abdomen and pelvis were obtained to include the region of the adrenal glands and ovaries. Studies were performed after administration of oral and intravenous contrast using contiguous 1-cm slices through the areas of interest. Abdominal and pelvic ultrasound was performed with a variety of commercially available realtime sector scanners using a 3.5- or 5-mHz transducer. These scans were usually limited to the lower pelvis with attention to the adnexal regions.

The NP-59 study was approved by the Human Studies Committee of the University of Michigan. The nature of the study was explained in detail to each patient and written consent was obtained. NP-59 scintigraphy was performed during a 3-7 day interval after injection of 1 mCi of the radiotracer. Dexamethasone, 4 mg daily in divided doses (1.0 mg q 6 hr), was administered orally for 7 days before NP-59 injection and throughout the 7-day postinjection interval (9). All patients were given stable iodide, Lugol's or saturated

potassium iodine solution for 24 hr prior to and for 10 days after scintigraphy. Bowel preparation with a mild laxative (bisacodyl, 10 mg BID) was also given orally 48 hr prior to and throughout the imaging intervals. If doubt remained as to NP-59 uptake being in ovary or bowel, imaging was repeated following additional laxative and enema administration (10). A gamma camera equipped with a high-energy, parallel hole collimator interfaced to a digital minicomputer was used to obtain 50,000 to 100,000 count images of the abdominal and pelvic regions. Serum testosterone, androstenedione, and DHEAS were measured by radioimmunoassay (11,12). Urine 17-ketosteroids were measured by fluorometric methods (13).

RESULTS

The response of androgen suppression after dexamethasone administration was obtained in Cases 3, 4, 5, and 7 through 9, (Table 1). The results showed failure of suppression of peripheral androgen levels in Patient 3 having a lipid cell tumor, but Patient 4 with polycystic ovarian disease (PCO), Patient 5 with hyperthecosis, and Patients 7-9 all demonstrated suppression of peripheral androgen levels after dexamethasone administration. In all cases, however, the ability to

TABLE 1
Summary of Clinical, Hormonal, Imaging Findings, and Diagnosis

Patient no.	Age/sex	Physical	Basal hormones values	CT or U/S	NP-59 DEX suppressed	Diagnosis
1	78/F	Hirsutism, virilization	Testosterone = 18.7 DHEAS = 4160 Androstenedione = 10.4	CT and U/S-3 cm left ovarian mass	Left pelvic uptake	3 cm left ovarian lipid cell tumor
2	34/F	Hirsutism, amenorrhea	Testosterone = 5.4 DHEAS = 577 Androstenedione = 9.1	CT- 4 cm left ovarian mass	Left pelvic uptake	4 cm left ovarian lipid cell tumor
3	36/F	Hirsutism, virilization	Testosterone = 15.4 DHEAS = 2292 17-Ketosteroid = 41.5	CT- 12 cm right ovarian mass	Right pelvic uptake	12 cm right ovarian lipid cell tumor
4	29/F	Hirsutism	Testosterone = 1.4 DHEAS = 6170	CT and U/S- 5 cm left ovarian mass	Left pelvic uptake	Polycystic ovarian disease 5 cm in size L ovary normal size R ovary
5	30/F	Marked virilization	Testosterone = 1.9 DHEAS = 1510 17-Ketosteroids = 15.0	U/S- 12 cm right ovarian mass	Bilateral ovarian uptake R > L	Hyperthecosis Bilaterally enlarged ovaries
6	69/F	Hirsutism	Testosterone = 4.0 DHEAS = 240 17-Ketosteroids = 6.2	CT - bilateral ovarian masses L > R	Bilateral ovarian uptake L > R	Hyperthecosis Bilaterally enlarged ovaries
7	55/F	Hirsutism, no other signs of virilization	Testosterone = 0.99 DHEAS = 5664 17-Ketosteroids = 14.2	Normal pelvic CT	Normal	Peripheral conversion
8	20/F	Hirsutism, obesity, acne	Testosterone = 0.50 DHEAS = 975 17-Ketosteroids = 11.8	Normal pelvic CT	Normal	Peripheral conversion and increased end organ sensitivity
9	41/F	Hirsutism, obesity	Testosterone = 0.1 DHEAS = 7355 17-Ketosteroids = 26.2	Normal pelvic CT and U/S	Normal	Peripheral conversion and increased end organ sensitivity
Normal range for hormone levels (Women)			Serum testosterone (.24-.66 ng/ml) Serum DHEA sulfate (820-3380 ng/ml)			Serum androstenedione (.3-.8 ng/ml) Urinary 17-ketosteroids (4-14 mg/total volume)

suppress peripheral androgens provided no anatomic localization information concerning the source(s) of excessive androgens.

NP-59 scintigraphy successfully imaged the sites of ovarian dysfunction in the six cases with proven ovarian disease (Table 1). The biochemical data of Cases 1 through 3 and the pelvic NP-59 scan of Case 3 have been presented in separate previous reports; (Refs. 5 and 14, respectively). Three patterns of NP-59 images were observed in the nine patients studied. In all cases, bowel activity was excluded as accounting for tracer accumulation by repeat imaging on Days 3 through 7, and demonstration of persistent and focal activity in the abnormal adnexal region(s).

Pattern 1: unilateral pelvic uptake. Four patients demonstrated this pattern; three were diagnosed as having unilateral, virilizing, lipoid cell tumors after surgical resection of the neoplasm and pathologic tissue examination. In all three patients with lipoid tumors of the ovary, each had marked elevation in serum testosterone (range 5.4–18.7 ng/ml) with ovarian masses depicted on CT and/or ultrasound and all demonstrated unilateral uptake of NP-59 on the side of the pelvis harboring the ovarian tumor. Figure 1A shows the abnormal CT scan of the lipoid cell tumor in Patient 2 (Table 1) with the corresponding abnormal NP-59 scan shown in Figure 1B. The fourth patient had PCO, (Patient 4, Table 1). Figure 2A shows the abnormal CT scan and Figure 2B shows the NP-59 scan in this case demonstrating marked asymmetric tracer uptake localized to the left pelvis. In this case the unilateral left ovarian uptake was expected since the right ovary had a normal CT appearance.

Pattern 2: bilateral pelvic uptake. Two patients demonstrated this pattern, both diagnosed at laparotomy with hyperthecosis (luteal cell hyperplasia). In these two patients (5 and 6, see Table 1) with luteal cell hyperplasia the CT scans were abnormal and the serum testosterone concentration was in the range regarded as diagnostic for virilizing tumors. The asymmetric (right > left) pattern of uptake correlated with the results of selective catheterization of the ovarian veins in Case 5, where a marked difference in ovarian effluent testosterone (right ovarian vein = 48.9 ng/ml, left ovarian vein = 9.8 ng/ml, peripheral vein = 1.9 ng/ml) was measured. In each case there was bilateral enlargement of both ovaries depicted on CT and/or ultrasound. This diffuse asymmetric pelvic uptake is exemplified by the anterior pelvic NP-59 scan of Patient 5, shown in Figure 3. This patient received repeated laxatives and enemas, and in all scintigraphs of the anterior pelvis the diffuse abnormal activity pattern was seen, indicating bilateral ovarian uptake, (R > L). This diffuse asymmetric pattern may be compared to Figure 4, in which no abnormal ovarian uptake was found.

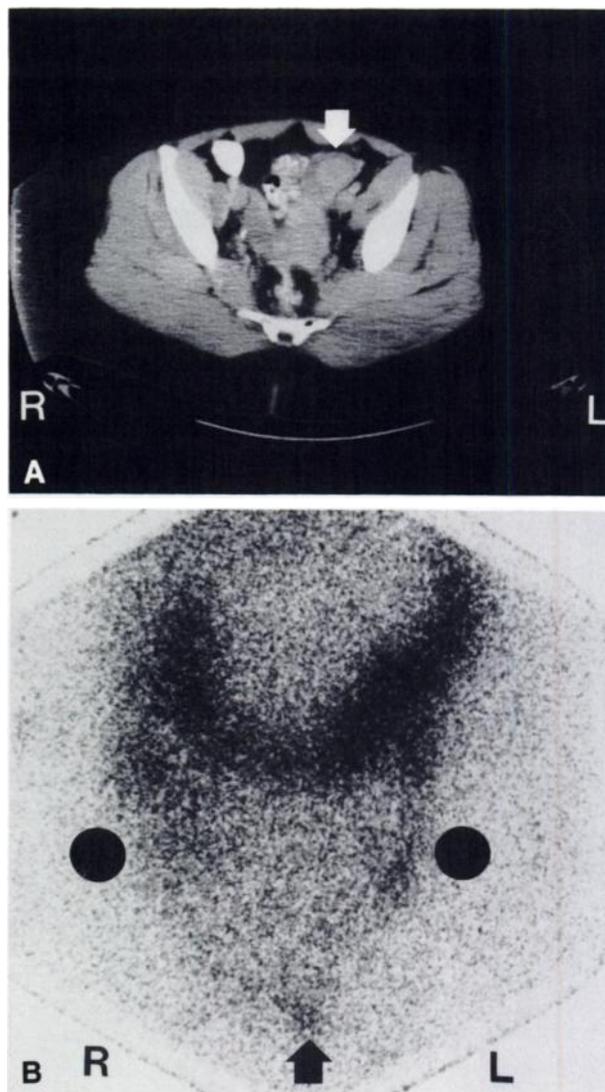


FIGURE 1

A: CT scan, transverse section through the level of the pelvis showing a left ovarian mass (arrow) representing the lipoid cell tumor in Patient 2 (Table 1). B: Anterior pelvic scan at 5 days post NP-59 injection. Abnormal activity in the region of the left pelvis (arrow) representing increased tracer uptake in the lipoid cell tumor. At laparotomy a 4.0 cm in diameter left ovarian lipoid cell tumor was found. Black circles mark the iliac crest.

Pattern 3: no definite pelvic uptake. In three of the cases (Patients 7–9, Table 1) without anatomic abnormalities of the adrenal or ovaries by CT or ultrasound examination and minimal clinical evidence of hirsutism, the testosterone levels were in the normal range or only slightly elevated (Table 1). There was accumulation of NP-59 in the adrenals, which appeared late: 5 days or more after dexamethasone suppression (DS), which is normal and no discernible NP-59 uptake in the pelvic region (Fig. 4), a normal finding on DS scintigraphy (7).

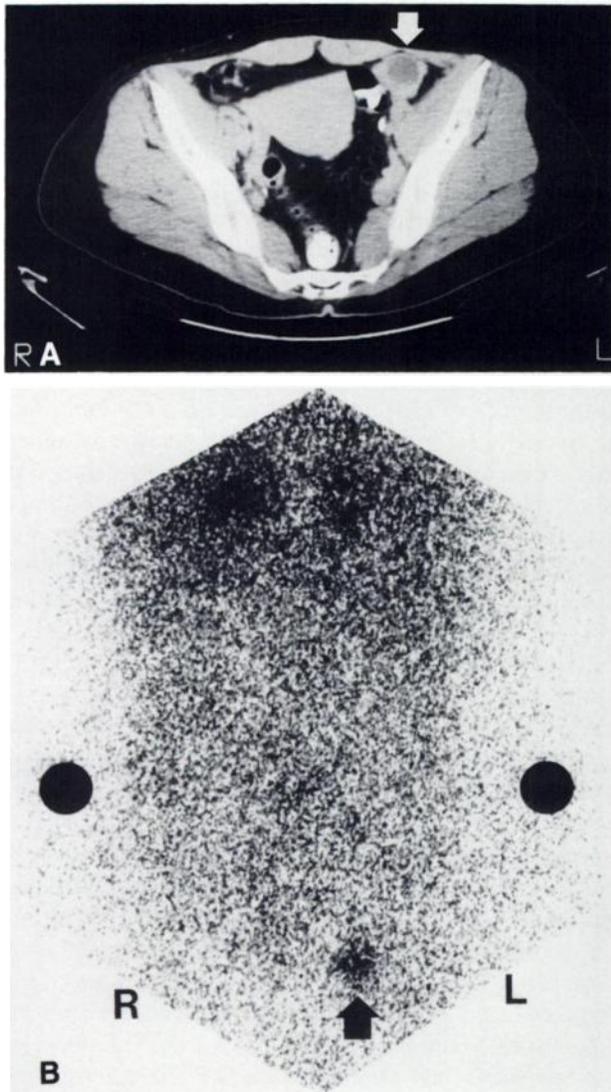


FIGURE 2
 A: CT scan transverse section through the level of the pelvis showing a left ovarian mass (arrow) in Patient 4 (Table 1) with polycystic ovarian disease. B: Anterior pelvic scan at 6 days post NP-59 injection. There is an area of increased tracer uptake localized to the region of the left ovary (arrow) representing increased uptake in the left polycystic ovary. At laparotomy an enlarged 5 cm in diameter cystic left ovary was found. Black circles mark the iliac crest.

DISCUSSION

Androgen-secreting ovarian neoplasms are rare, and often present difficult diagnostic problems. The results of hormonal stimulation and suppression tests are frequently unable to discern the origin(s) of abnormal hormonal secretion in women with HA (15,16) since many ovarian and adrenal neoplasms respond similarly to both gonadotropin and adrenocorticotropin stimulation and suppression maneuvers (17). There is lack of specificity of the traditional endocrine function tests

to determine the site of HA (18) and even the combination of hormonal tests and anatomic imaging may fail to discern an abnormally functioning gland(s), and at times can be frankly misleading (19). Since precise differentiation of ovarian from other sources of androgen hypersecretion is required for the optimal management of these patients, direct hormone levels obtained by selective catheterization of the venous effluent from the ovary and adrenal glands may be the most accurate method to discern the correct etiology of HA in many cases (20). Although this approach is successful in localizing the source(s) of HA, it is technically demanding, and invasive. Successful sampling from both adrenal and both ovarian veins can be achieved in not more than 75–80% of attempted cases (6).

High resolution CT and abdominal ultrasound are useful, but successful localization by each is dependent upon changes in organ anatomy and contour, (usually enlargement of the ovaries in the cases discussed here) sufficient to identify tumorous involvement. This approach depicts abnormal anatomy, but because there is much variability in size and configuration of the normal adrenal and nonfunctional adrenal mass (21,22) as well as the normal and abnormal ovary (23,24) enlargement does not necessarily correlate with the degree or presence of a functional abnormality.

Scintigraphic localization of ovarian dysfunction has been suggested in previous case reports and small series

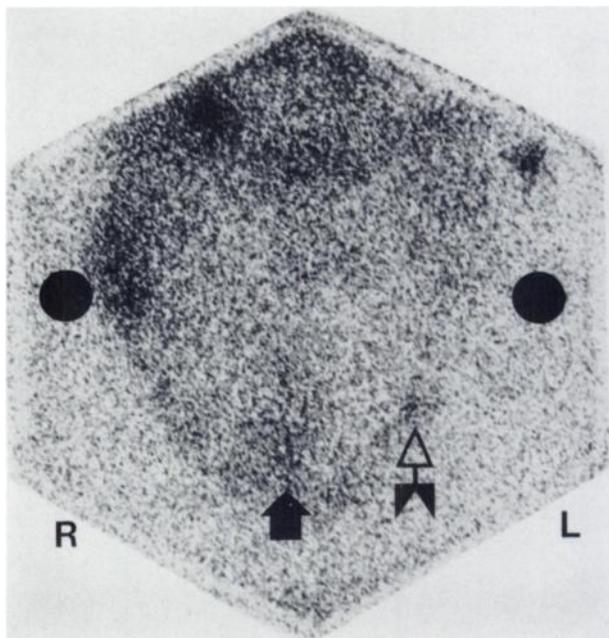


FIGURE 3
 Anterior pelvic scan at 6 days post NP-59 injection. There is bilateral ovarian uptake right (arrow) greater than left (open arrow), in Patient 5 representing bilateral ovarian hyperthecosis. At laparotomy an enlarged 12 cm in diameter right ovary and 4 cm in diameter left ovary was found. Black circles mark the iliac crest.

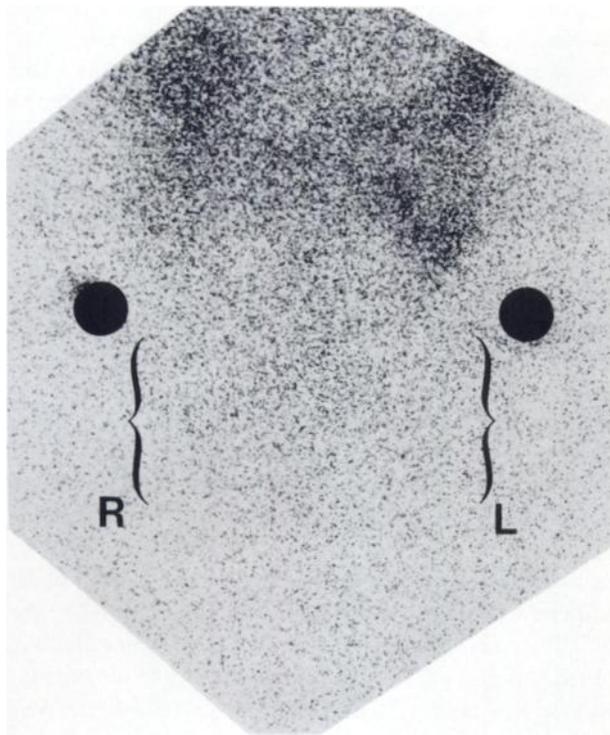


FIGURE 4
Anterior pelvic NP-59 scan at 6 days post NP-59 injection. Normal scan findings in Patient 8 after vigorous bowel cleansing showing no discernible tracer uptake in the pelvic region (brackets). Black circles mark the iliac crest.

(5,14,25). The rationale for the imaging of gonadal tissues is an extension of that of adrenal accumulation of NP-59. Gonadal steroid-producing tissues, like the adrenal, express the lipoprotein receptors necessary for the internalization of cholesterol contained within circulating lipoproteins (26,27). It is through this receptor-dependent pathway that the bulk of cholesterol (and NP-59) for steroidogenesis is made readily available to these tissues (26,27). We have demonstrated in adrenal tissues that once incorporated within the cholesterol ester storage pool, NP-59 is not further metabolized to steroid hormones and thus, it remains as a marker of substrate accumulation (28).

To date the major thrust of imaging using NP-59 in HA has been performed primarily for the noninvasive evaluation of adrenal involvement in this syndrome (9). The accumulation of NP-59 into both tumorous and hyperplastic adrenal glands has correlated with 17-ketosteroid excretion, a measure of hormonal dysfunction (29). As these previous studies were designed to evaluate adrenal function, adequate and persistent bowel preparation was not incorporated into their protocols, which may serve to explain the absence of discernible ovarian accumulation of NP-59 seen in patients with PCO both on and off prior dexamethasone suppression (7,29). The importance of adequate bowel

preparation and, if necessary, delayed imaging in the evaluation of pelvic NP-59 uptake cannot be overemphasized (10). Moreover, in milder forms of PCO the dysfunctional state of the ovaries may not be sufficient to accumulate adequate NP-59 for discernible visualization. Taylor et al. (5) reported an inability to visualize proven bilateral ovarian hyperthecosis in two patients on NP-59 scanning. This may be because of inadequate bowel preparation, since in the two cases reported here, vigorous bowel preparation was performed and pelvic uptake was seen in each case (10). A critical level of anatomic abnormality characterized by CT and/or ultrasound in PCO and hyperthecosis and abnormal hormone secretion by the ovary in these and other tumorous ovarian conditions would be necessary for successful localization by scintigraphy. Rare reports of ovarian tumors accumulating sufficient NP-59 for imaging have appeared in the literature, but to date these have been case reports of incidental observations (14, 30).

In the present series we have characterized and evaluated NP-59 imaging in nine women clinically suspected of having an ovarian source of HA. Although the numbers of patients studied is small, and a statistical evaluation of efficacy cannot be made, in this particular group, four etiologies of HA that span much of the spectrum of HA were evaluated. One cause of HA found in three women in this series who demonstrated unilateral uptake of NP-59 was the result of lipoid cell ovarian tumors. All of these women had marked elevation of serum testosterone levels. All subsequently underwent surgical exploration and resection of the tumor after an anatomically abnormal ovary was found. One woman in our series had endocrine studies characteristic of PCO (31-33), and asymmetric NP-59 uptake was localized to the left pelvis. An enlarged left ovary was confirmed on the CT scan and at subsequent laparotomy. Two patients with luteal cell hyperthecosis showed a pattern of NP-59 uptake characterized by diffuse but asymmetric pelvic uptake and in one of these women selective ovarian vein hormone sampling corroborated the NP-59 findings. Thus, NP-59 correctly identified the ovary as the primary contributing source of androgens in this woman. This may be of importance, since unilateral oophorectomy has been recommended in asymmetric hyperthecosis to remove the predominant source of androgens; such therapy has been followed by restoration of menses and amelioration of hirsutism while maintaining fertility (34,35).

In each case the NP-59 scan, either by the presence of unilateral (in ovarian tumors and PCO), or bilateral (in hyperthecosis) uptake depicted ovarian dysfunction. Moreover, in the two cases of hyperthecosis NP-59 not only confirmed the anatomic abnormality, but also correctly identified the asymmetric nature of the ovarian disease (Table 1). The final group was comprised of

three women with mild signs of hirsutism who were suspected by physical and hormonal examination to have lesser degrees of ovarian dysfunction. The NP-59 scan and pelvic CT were normal suggesting either peripheral conversion of androgen precursors or increased end organ sensitivity as possible explanations for the mild hirsutism in these women. Confirmation from selective ovarian and adrenal vein catheterization was not performed as this procedure is usually reserved for patients with greater degrees of hormonal abnormality and virilization. Furthermore, follow-up for a period of 4 to 7 yr has not lead to modification of the clinical diagnoses in these cases.

The scintigraphic approach provides functional information that is not available by other noninvasive radiographic techniques. It has been previously suggested that, with the exception of the patient with a diagnosis of congenital adrenal hyperplasia, virilized women may benefit from NP-59 scintigraphy (7). This procedure however, due to its relatively unfavorable dosimetry (~6–8 rad/mCi ovary exposure, 1 rad/mCi, total body) (36), should not be used as a screening modality but be reserved for women with clinical and biochemical findings compatible with definite ovarian and/or adrenal dysfunction. If all these findings (including scintigraphy) remain nondiagnostic then selective adrenal and/or ovarian venous catheterization and sampling could be performed in an attempt to locate the source(s) of HA. Our data suggest that the NP-59 scan may be used to advantage in some cases to supplement the anatomic information of CT and/or ultrasound in the evaluation of ovarian androgen secretion and dysfunction in the virilized woman.

ACKNOWLEDGMENTS

The authors thank Ms. Michele Curro and Mrs. Annise L. Johnson for their expert secretarial assistance. They also acknowledge the assistance of Dr. T. Mangner and H. Anderson-Davis for the synthesis of NP-59, and the Phoenix Memorial Laboratories for the use of their radiochemical facilities. This work was supported by Grants—NCL(CA-09015), NIAMDD (R01-AM-21477RAD), GCRC(HEW3M01-RR-0042-21CLR), NIH (R01-CA-43300-01) and the Nuclear Medicine Research Fund.

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