A case of lean polycystic ovary syndrome with early stage of type 1 diabetes successfully treated with metformin

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Abstract. Polycystic ovary syndrome (PCOS) is common in obese women with insulin resistant type 2 diabetes for which metformin treatment is getting established in addition to clomiphene. However, lean PCOS patients are sometimes accompanied with type 1 diabetes. It remains unclear whether these patients are insulin resistant and whether metformin is effective for them. A 32-year-old woman, who suffered from acne, hirsutism, and menstrual disorders since age 29, was diagnosed as PCOS by serum high LH levels and polycystic ovary on echography. Interestingly, her body mass index (BMI) had consistently been 21.0 kg/m² since age 20. She was first treated with clomiphene for one year for infertility but it did not improve her menstrual cycle nor did she get pregnant during that period. She was then assessed with diabetes mellitus and subsequently diagnosed as type 1 diabetes with mild hyperglycemia (HbA1c 6.0%). Since her insulin secretion was still well preserved, to assess insulin sensitivity, hyperinsulinemic-euglycemic clamp test was performed and showed her to be insulin resistant. Low dose insulin and low dose metformin treatment was started without clomiphene. After her ovulation and menstrual cycle were ameliorated only one month later, her treatment was supplemented with clomiphene for the next three months enabling her to at last become pregnant. This report highlights the efficacy of metformin in lean PCOS with type 1 diabetes. Insulin therapy is essential for type 1 diabetes but hyperinsulinemia potentially exacerbates PCOS through hyperandrogenism. Metformin is therefore recommended for treatment of lean PCOS with type 1 diabetes as well as common obese PCOS with type 2 diabetes.

Key words: Lean, Polycystic ovary syndrome, Type 1 diabetes, Insulin resistance, Metformin
consistently been 53 kg (body mass index (BMI): 21.0 kg/m²) since age 20, indicating the absence of obesity and suggesting the lack of insulin resistance. Based on fasting (at plasma glucose 94 mg/dL) and postprandial (at plasma glucose 163 mg/dL) C-peptide levels (1.14 and 2.55 ng/dL, respectively) and fasting insulin level (3.9 μU/mL), she did not seem to be severely insulin resistant nor lacking in insulin secretion. However, islet autoantibody was positive for glutamic acid decarboxylase (GAD)-65 (40.0 U/mL; normal range <1.5 U/mL). Therefore, her most probable diagnosis was early stage type 1 diabetes, as distinct from type 2 diabetes by the presence of islet autoantibodies.

Out of her desire to become pregnant she wanted to receive metformin treatment for her PCOS and diabetes after her search on website. Although her homeostatic model assessment of insulin resistance index (HOMA-IR) and Matsuda index were normal (1.0 mg/dL×μU/mL and 4.79, respectively), hyperinsulinemic-euglycemic clamp test (insulin infusion rate; 40 mU/m²/min), which is the world-wide golden standard test for the evaluation of insulin sensitivity, showed her glucose infusion rate (GIR) was 265.5 mg/m²/min, which suggested moderate insulin resistance [1]. Assessment of insulin secretion and insulin resistance is summarized in Supplementary Fig. 1.

Therefore, in addition to insulin therapy, which is the standard therapy for type 1 diabetes, metformin was started in hopes of improving both PCOS and insulin resistance. Because her HbA1c was 6.0% and body weight was 53 kg, the starting dose was insulin lispro (2-0-2) units for each meal and metformin 500 mg/day. Her matured follicle was observed on day 25 in menstrual cycle before the treatment, but since it was improved on day 15 one month after metformin treatment was begun, it appeared that metformin improved her menstrual disorder. Consistent with this improvement, LH level was decreased to 7.5 mIU/mL. Metformin treatment was then supplemented with clomiphene for three months at which point our patient finally succeeded in getting pregnant. In this course, glucose control level was kept in good condition (HbA1c ~5.9% with insulin aspart (2-2-3) units and metformin 500 mg/day). The summary of her clinical history is shown in Fig. 1.

Discussion

We experienced a case of lean PCOS with type 1 diabetes that was successfully treated with metformin about irregular ovulation, menstrual disorder, and infertility.

Although her androgen levels were normal (Supplementary Table 2), hyperandrogenic signs such as acne and hirsutism were observed. To diagnose PCOS exactly, differential diagnosis should be performed to exclude other conditions such as Cushing syndrome, congenital adrenal hyperplasia, and recovery period from amenorrhea due to weight loss. Cushing syndrome was excluded based on the lack of typical signs such as moon facies, visceral adiposity, skin thinning, and proximal muscle weakness, as well as absence of increased white blood cell count, no abnormalities in electrolytes, and normal levels of ACTH and cortisol. Congenital adrenal hyperplasia such as 21-hydroxylase deficiency and 3β-hydroxysteroid dehydrogenase deficiency was excluded based on normal levels of testosterone and dehydroepiandrosterone sulfate (DHEA-S) (no hyperandrogenemia), no symptoms of adrenal deficiency, and normal ACTH level, as well as no hyperpigmentation and no abnormality of external genitalia. Recovery period from amenorrhea due to weight loss was excluded based on no history of extreme body weight loss which causes menstrual disorders.

Her etiology of diabetes seemed to be early stage type 1 diabetes because the anti-GAD-65 antibody was positive and insulin secretion was preserved. Interestingly, insulin resistance existed judging from her glucose clamp results even though her BMI was low and she lacked the signs of metabolic syndrome such as central obesity, hypertension, and dyslipidemia. From these findings we concluded that her insulin resistance was probably due to PCOS. GIRs measured using the same clamp protocol were reported to be 339±76, 270±66, 264±66, and 175±96 mg/m²/min (mean±SD) for lean controls, lean PCOS, overweight controls, and overweight PCOS, respectively [1]. In our case, GIR was 265.5 mg/m²/min, which suggests insulin resistance similar to the level of overweight controls compared to non-PCOS lean control (339±76 mg/min/m²). Not only BMI but also HbA1c and HOMA-IR were within normal range in our case, but these parameters were also consistent with the values in the same previous report, namely, BMI was 22±2, 23±2, 35±6, and 36±7, HbA1c was 4.7±1.2, 5.0±0.1, 5.4±0.3, and 5.4±0.4%, and HOMA-IR was 0.8±0.3, 0.8±0.3, 4.4±2.6, and 6.3±3.2 mg/dL×μU/mL (mean±SD), respectively, in each of the above groups.
Metformin for lean PCOS with type 1 DM

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It is reported that hyperinsulinemia caused by subcutaneously injected insulin results in hyperandrogenism [2]. The prevalence of PCOS in Japanese women with type 1 diabetes is reported as 27.2% in a previous report [3]. Therefore, hyperinsulinemia-euglycemic clamp test is most suitable to detect insulin resistance in lean PCOS patients, specifically in type 1 diabetes, and actually our case was insulin resistant whereas HOMA-IR index was normal. The difference between HOMA-IR and GIR might be due to the difference in methods. HOMA-IR is calculated from fasting plasma insulin and glucose concentration, which might lead to lower values in patients with type 1 diabetes whose endogenous insulin secretion is decreased. In contrast, GIR is assessed in the hyperinsulinemic condition by exogenous high dose insulin infusion, which could exclude the factor of endogenous insulin secretion.

It is reported that the onset of PCOS is often later than that of diabetes [2]. In patients with type 2 diabetes mellitus, it is well-known that hyperinsulinemia caused by insulin resistance promotes androgen secretion from the liver and ovaries, and in turn hyperandrogenemia causes menstrual disorders and polycystic changes of ovaries. Meanwhile, in patients with type 1 diabetes mellitus, it is reported that hyperinsulinemia caused by subcutaneously injected insulin results in hyperandrogenism [2]. The prevalence of PCOS in Japanese women with type 1 diabetes is reported as 27.2% in a previous report [3]. Therefore, PCOS could be caused by hyperinsulinemia in both insulin resistant type 2 diabetes and insulin treated type 1 diabetes, and the onset of hyperandrogenism is often later than that of diabetes [2]. However, in this case, it is interesting that she already had symptoms of hyperandrogenism even though she never received insulin therapy or suffered from insulin resistance by obesity. Her insulin resistance seemed to be caused by PCOS secondarily.

In general, the initial treatments recommended for ovulatory disorder in PCOS are beneficial lifestyle modifications such as changes in diet and exercise. When these treatments are ineffective, pharmacological therapies are recommended. Although clomiphene is typically prescribed for ovarian dysfunction, it has been reported that metformin is also beneficial.

![Fig. 1 Summary of clinical history](image)

BMI has been consistently 21 kg/m². She had hyperandrogenic signs and was diagnosed as PCOS. Clomiphene was ineffective for one year. She was then diagnosed as type 1 diabetes. Glycemic control was very good (HbA1c ~6.0 %), but she was moderately insulin resistant as assessed by hyperinsulinemic-euglycemic clamp. Metformin treatment was started combined with low dose insulin. Only one month later menstrual disorder was improved and the following combination therapy with clomiphene for three months brought her pregnancy.
for restoring ovarian function such as ovulation and menstrual cycle in PCOS patients with type 2 diabetes mellitus [4, 5], because metformin improves insulin sensitivity and hyperandrogenism [6, 7]. Metformin is therefore recommended for PCOS patients by the American Association of Clinical Endocrinologists [8]. Recently even in non-obese women with PCOS, metformin treatment was shown to be beneficial for infertility through a systematic review and meta-analysis [9]. However, it is also reported that lean PCOS patients (BMI<25) were nonresponders to metformin for improvement of menstrual abnormalities [10]. Furthermore, there are no specific regimens regarding medical treatment for ovarian function in lean PCOS patients with type 1 diabetes mellitus. Insulin therapy is necessary to protect pancreas and preserve insulin secretion in type 1 diabetes, but high dose insulin is not recommended because hyperinsulinemia causes hyperandrogenism [2]. The addition of metformin to an insulin regimen might reduce the necessary insulin dose and effectively improve hyperandrogenic symptoms in PCOS patients with type 1 diabetes. Our patient was therefore treated with low dose insulin and metformin combination therapy. Because the previous clomiphene treatment for one year was ineffective, clomiphene was not combined to metformin for the first month. Fortunately, the insulin and metformin combination therapy without clomiphene was sufficient to ameliorate ovulation and menstrual disorder. In hopes of achieving pregnancy, we then added clomiphene to the above treatment protocol based on previous reports of the stronger efficacy of metformin and clomiphene combination therapy compared to clomiphene or metformin monotherapy [6, 11]. Three months later our patient became pregnant. Because hyperinsulinemic-euglycemic clamp study could not be repeated due to ethical reasons, it is unclear that the beneficial effects of metformin on PCOS were through amelioration of insulin resistance, but amelioration of insulin resistance might also have contributed to pregnancy to some extent. However, post-treatment HOMA-IR, HbA1c, and body weight were comparable to the pretreatment condition, which suggests that pregnancy might have been induced by metformin beyond amelioration of insulin resistance. Further investigations through large clinical trials on the effectiveness and mechanisms of metformin in lean PCOS patients with type 1 diabetes are necessary in the future.

**Conclusion**

Metformin was effective in the treatment of a lean PCOS patient with type 1 diabetes. Insulin therapy is essential for type 1 diabetes but hyperinsulinemia potentially exacerbates PCOS through hyperandrogenism. Therefore, metformin treatment is recommended for lean PCOS with type 1 diabetes as well as for common obese PCOS with type 2 diabetes.

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**Supplementary Table 1 Laboratory data - 1**

| Parameter | Value |
|-----------|-------|
| Na        | 141 mM |
| K         | 3.8 mM |
| Cl        | 107 mM |
| Tp        | 6.8 g/dL |
| Alb       | 4.2 g/dL |
| BUN       | 14 mg/dL |
| Cre       | 0.68 mg/dL |
| eGFR      | 80.9 mL/min/1.73m² |
| UA        | 5.0 mg/dL |
| GOT       | 13 U/L |
| GPT       | 14 U/L |
| LDH       | 135 U/L |
| ALP       | 140 U/L |
| TC        | 206 mg/dL |
| HDL-C     | 73 mg/dL |
| LDL-C     | 123 mg/dL |
| PG        | 94 mg/dL |
| IRI       | 3.5 µIU/mL |
| CPR       | 1.14 ng/mL |
| HbA1c     | 5.9 % |
| WBC       | 6,500 /µL |
| RBC       | 438 x 10⁶ /µL |
| Hb        | 12.9 g/dL |
| Ht        | 38.1 % |
| Plt       | 211 x 10¹² /µL |

**75g oral glucose tolerance test**

| Time  | PG (mg/dL) | IRI (µIU/mL) |
|-------|------------|---------------|
| 0 min | 108        | 5.5           |
| 30 min| 220        | 21.8          |
| 60 min| 275        | 34.6          |
| 90 min| 275        | 42.4          |
| 120 min| 235      | 45.5          |

**GAD antibody**

40 U/mL

**Glucagon**

150 pg/mL

**Urinary CPR**

40.0 µg/day

**Urinary Alb**

2.2 mg/gCr

**CCr**

123.8 mL/min/1.73m²

**Urinary volume**

1,800 mL

Biochemical data including 75g OGTT are shown in this table. (Red: above normal range, blue: below normal range)
Supplementary Table 2  Laboratory data - 2

| Parameter                  | Value       | Normal Range |
|----------------------------|-------------|--------------|
| LH                         | 9.0 mIU/mL  |              |
| FSH                        | 4.6 mIU/mL  |              |
| DHEA-S                     | 263 μg/dL   |              |
| Free testosterone          | <0.6 pg/mL  |              |
| Androstenedione            | 2.33 ng/mL  |              |
| Estradiol (ovulatory phase)| 363.2 pg/mL |              |
| Progesterone (luteal phase)| 13.86 ng/mL |              |
| Pregnenolone               | 0.57 ng/mL  |              |
| PRL                        | 14.4 ng/mL  |              |
| ACTH                       | 13.6 pg/mL  |              |
| Cortisol                   | 7.4 μg/dL   |              |
| Renin activity             | 1.4 ng/mL/ hr|              |
| Aldosterone                | 219 pg/mL   |              |
| F-T3                       | 2.29 pg/mL  |              |
| F-T4                       | 1.16 ng/dL  |              |
| TSH                        | 1.10 μIU/ml |              |
| Thyroglobulin              | 9.41 ng/mL  |              |

| Parameter                  | Value       | Normal Range |
|----------------------------|-------------|--------------|
| Urinary 17-ketosteroids, 7 fractions |  |              |
| Androsterone               | 1.24 mg/gCr |              |
| Etioclanolone              | 2.03 mg/gCr |              |
| Dehydroepiandrosterone     | 0.39 mg/gCr |              |
| 11-ketoandrostenedione     | 0.06 mg/gCr |              |
| 11-ketoetiocholanolone     | 0.45 mg/gCr |              |
| 11-hydroxyandrostenedione  | 0.68 mg/gCr |              |
| 11-hydroxyetiocholanolone  | 0.45 mg/gCr |              |

Hormone data are shown in this table and also pictures of ovary ultrasonography are attached here.
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