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Original article

Surprisingly low infertility rate in married type 2 diabetic women: A rather curious paradox to the current opinion of insulin resistance as the joint pathogenesis of poly cystic ovary syndrome and type 2 diabetes mellitus

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ABSTRACT

Back ground: Sharing the same pathophysiologic principle which is insulin resistance, type 2 diabetes mellitus (T2DM) and poly cystic ovary syndrome (PCOS) are usually considered closely related and easily interchangeable medical entities. Numerous attempts have been made to document this illusory perspective.
Objective: Based on a delicate pathophysiologic notion, we believe that fully developed T2DM is infrequently observed with fully featured PCOS.
Materials and methods: In an observational descriptive study 257 married T2DM women were consecutively included and meticulously investigated for fertility history and, albeit, clinical and biochemical features of PCOS.
Results: Of 257 married diabetic women only six (2.3%) had no children. In one case a male problem (azoospermia) and in the second case, late marriage (aged 45 at wedding ceremony) was the cause of infertility. Thus, only four (1.6%) might have been labeled as true female factor infertility. Astounding to report was the average pregnancies for each participant which was 5.1 ± 2.5, ranging from zero to fifteen.
Conclusion: we would suggest that, despite the well-established fact of insulin resistance as the common pathophysiologic process for T2DM and PCOS, they are definitely separate medical entities. As a matter of fact T2DM and PCOS are the two opposite aspect of the insulin resistance coin.
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Introduction

The poly cystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935 as a distinct medical entity encompassing the amenorrhea, hirsutism and obesity in a setting of bilateral large pearly white, poly cystic ovaries [1]. Currently, according to Rotterdam Consensus meeting, in the absence of any other obvious cause of androgen excess, the presence of two out of the following three criteria would establish the clinical diagnosis of PCOS.

- Oligoamenorrhea as the clinical indication of oligo- and/or anovulation.
- Clinical and/or biochemical manifestations of hyperandrogenism, i.e. hirsutism, androgenic alopecia, increased serum weak androgens or testosterone.
- Poly cystic ovaries by preferably transvaginal ultrasound [2].

PCOS is probably the most common reproductive endocrinologic disorder of women. Depending upon the different diagnostic criteria and in unselected groups, 6–12% of reproductive aged women are believed to be affected by PCOS [3–5]. Over the last eight decades a wide variety of pathogenetic explanations have been proposed for the Perplexing clinical and biochemical manifestations of PCOS. A cluster of abnormal intrinsic ovarian steroidogenic defects, functional ovarian/adrenal gland hyperandrogenism, and finally some extrinsic factors were proposed to be

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contributed to the overall dysregulated steroidogenesis and chronic anovulation as the two basic features of PCOS. Although, they are all precious and appreciably informative in due course, but none of them were either comprehensive or reasonably fruitful towards the clinical management of the disorder. This line of research was obviously incoherent until the noble concept of insulin resistance, compensatory hyperinsulinemia and delicate insulin/IGF-1 receptor interaction in the ovaries was put in the lime light [6–8]. The well-established effectiveness of insulin sensitizers (Metformin and Glitazones) in inducing ovulation in PCOS subjects concretely endorsed the above issue [9,10]. As soon as the concept of insulin resistance was proposed as the fundamental pathogenetic process of PCOS, the medical literature received a massive flood of papers suggesting the clinical, biochemical, metabolomic and proteomic overlaps between type 2 diabetes mellitus (T2DM) and PCOS [11–14]. Of all those reports, the ones that refer to the relatively small long-term risk of impaired glucose tolerance (IFG) or mild T2 DM in PCOS subjects could be favourably considered and believed to be fairly logic. But, the published papers addressing the high prevalence of PCOS in fully developed, middle-aged T2DM cases are to be revised and critically questioned [15–16]. As Ovall and Azziz cleverly hinted years ago, we also suggest that, T2DM and PCOS are two different and reasonably distinct aspects of a common insulin resistance coin. In order to evaluate the trues and tricks concerning our suggestion and to clarify this complex issue, we designed and conducted the present study.

Methods

In an observational, merely descriptive study, 256 married T2DM women consecutively attending a university hospital diabetes clinic were given enough information towards the research project and those who were deeply interested to participate were included. The basic aim of the study was to elucidate the fertility potentials in women who had developed full-blown T2DM. An experienced reproductive endocrinologist patiently interviewed and thoroughly examined the participants. Age, duration of diabetes, age at menarche, age at marriage, age at first pregnancy, number of pregnancies, history of chronic oligomenorrhea or amenorrhea (particularly during the first post-pubertal decade), history of any gynecologic consultations (apart from the deliveries), history of delayed fertilities or taking any kind of ovulation induction drugs were all recorded. Anthropometric parameters including weight, height, BMI and waist circumference were properly measured. Androgenic alopecia and hirsutism were assessed according to Norwood classification system and Gallway scoring table, respectively. Infertility was defined as one year of unprotected regular intercourse without conception. Oligomenorrhea was defined as menstrual cycles of longer than 6 weeks and lack of menstruation for more than three consecutive months was labeled as amenorrhea. Data were captured and analysed by SPSS version 19. Results were reported as meant ± standard deviation (S.D.) for the quantitative variables and percentages for the categorical parameters.

Results

The average age of participants was 53.9 ± 9.7 years, ranged 25–76 years (Table 1). Mean duration of T2DM was 6.8 ± 5.9 years with the range of 1–26 years (Table 1, Fig. 2). With regard to anthropometric measurements, mean of BMI turned out to be 28 ± 4.6, ranged 17.6–44.1 (Table 1, Fig. 3). The mean waist circumference was 94 ± 11 cm, ranged from 68 to 156 cm. Menarche had been experienced at mean age of 13.3 ± 1.6 years ranged 9–19 years (Table 1). In terms of clinical manifestations of androgen excess, 13 had hirsutism (5.1%) and five had present or past history of disfiguring acne (2%). Based on Norwood's androgenic alopecia classification, only 2 cases fulfilled class 2 and above of baldness (less than 1%). The history of recurrent and prolonged oligoamenorrhea were present in just 10 (4%). Looking into the other features of metabolic syndrome, 32.8% had concomitant hypertension and 31.6%were dyslipidemic. Concerning the most interested parameter, that is, pregnancy rate, 98.4% of the evaluated T2DM ladies had children (Fig. 5). It sounded interesting to report that the average number of pregnancies for each participant was 5.1 ± 2.5, ranged from zero to fifteen pregnancies (Fig. 1). As a matter of fact, of 256 T2DM married women only six had no children after one year or longer of unprotected regular intercourse (over-all infertility rate of 2.3%). On further review of the small infertile group, in one case, infertility was due to an obvious male problem (azoospermia), in the second case, late marriage (aged 45 on wedding ceremony) coinciding with protracted dysfunctional uterine bleeding (DUB) was the major obstacle for having baby. Only four out of 256 cases (1.6%) were to be firmly labeled as female-factor infertility (Fig. 5). The age range at first pregnancy varied from 12 to 29 years with a mode of 15–20 years. According to this simple but purposeful study the overall infertility rate was shown to be 2.3% in this particular diabetic population (Fig. 4). This figure is in frank contrast to the current infertility rate of 12–15% in general population. The ease and simplicity of study design cleans out any uncertainty concerning the structure of the presented research work. Thus, instead of being perplexed and feel confused about the results, one would rather wash away some of the sprung up misconceptions concerning the pathophysiologic link between T2DM and PCOS.

Table 1
Average age of participants, mean duration of T2DM, BMI, menarche, number of pregnancies and mean waist circumference.

	Mean	SD	Maximum	Minimum
Average age of participants	53.9	9.7	76	25
Mean duration of T2DM	6.8	5.9	26	1
BMI	28	4.6	44.1	17.6
Menarche	13.33	1.6	19	9
Number of pregnancy	5.12	2.5	15	0
Mean waist circumference	94 cm	11 cm	156 cm	68 cm

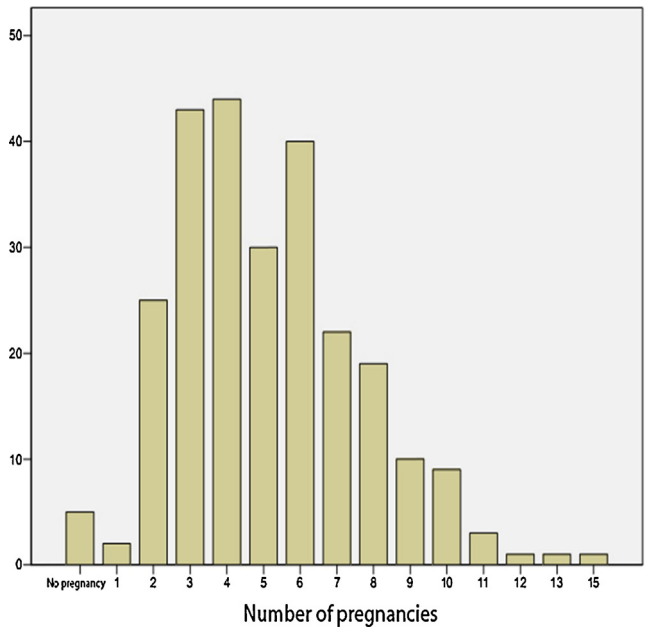

Fig. 1. Number of pregnancies.

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