Type 1 Diabetes and Polycystic Ovary Syndrome: Systematic Review and Meta-analysis

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BACKGROUND

A few small studies have reported increased prevalences of polycystic ovary syndrome (PCOS) and symptoms of androgen excess in women with type 1 diabetes.

PURPOSE

We performed a systematic review and meta-analysis of studies evaluating androgen excess symptoms and PCOS in women with type 1 diabetes.

DATA SOURCES

The Entrez-PubMed and Scopus electronic databases were used.

STUDY SELECTION

We selected studies addressing androgen excess signs, symptoms, and disorders in girls, adolescents, and adult women with type 1 diabetes.

DATA EXTRACTION

The main outcome measures were prevalences of PCOS, hyperandrogenemia, hirsutism, menstrual dysfunction, and polycystic ovarian morphology (PCOM).

DATA SYNTHESIS

Nine primary studies involving 475 adolescent or adult women with type 1 diabetes were included. The prevalences of PCOS and associated traits in women with type 1 diabetes were 24% (95% CI 15–34) for PCOS, 25% (95% CI 17–33) for hyperandrogenemia, 25% (95% CI 16–36) for hirsutism, 24% (95% CI 17–32) for menstrual dysfunction, and 33% (95% CI 24–44) for PCOM. These figures are considerably higher than those reported earlier in the general population without diabetes.

LIMITATIONS

The data collected in the original studies were heterogeneous in age, race, ethnicity, and criteria used for the diagnosis of PCOS; yet, we used a quality-effects model in the meta-analyses to overcome this limitation.

CONCLUSIONS

PCOS and its related traits are frequent findings in women with type 1 diabetes. PCOS may contribute to the subfertility of these women by a mechanism that does not directly depend on glycemic/metabolic control among other negative consequences for their health. Hence, screening for PCOS and androgen excess should be included in current guidelines for the management of type 1 diabetes in women.

REVIEW

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, showing a 6–15% prevalence worldwide (1). PCOS is currently perceived as a multifaceted and heterogeneous disorder that exposes affected women to considerable cosmetic, reproductive, metabolic, and cardiovascular risks and negatively affects their quality of life (2).

Even though PCOS is mainly an androgen excess disorder, insulin resistance and compensatory endogenous hyperinsulinemia, in close association with obesity and abdominal adiposity, are implicated in the pathogenesis of PCOS in many patients (3,4). In agreement, women with PCOS are at high risk for developing type 2 diabetes and gestational diabetes mellitus (3). Hyperinsulinemia enhances androgen synthesis and secretion by the ovaries by acting as a cogonadotropin (3), as demonstrated by the finding of a reversible PCOS-like phenotype in women with hyperinsulinemic conditions such as portosystemic shunt (5), insulinoma (6), or severe obesity (7).

Type 1 diabetes is a disease produced by an autoimmune injury to the endocrine pancreas that results in the abolition of endogenous insulin secretion. We hypothesized 15 years ago that PCOS could be associated with type 1 diabetes (8). The rationale was that women with type 1 diabetes needed supraphysiological doses of subcutaneous insulin to reach insulin concentrations at the portal level capable of suppressing hepatic glucose secretion, thus leading to exogenous systemic hyperinsulinism. Exogenous hyperinsulinism could then contribute to androgen excess in predisposed women, leading to PCOS as happens in insulin-resistance syndromes.

We subsequently published the first report of the association of PCOS with type 1 diabetes consisting of the finding of a threefold increase in the prevalence of this syndrome compared with that of women from the general population (8) and that the ovary was the most likely source of androgen excess in these women (9). Of note, even though this association was confirmed by all of the studies that addressed the issue thereafter (10–16), with prevalences of PCOS as high as 40% in some series (10,16), this syndrome is seldom diagnosed and treated in women with type 1 diabetes.

With the aim of increasing awareness of the frequent association of PCOS with type 1 diabetes, we have conducted a systematic review and meta-analysis of the prevalence of PCOS and associated hyperandrogenic traits in adolescent and adult women with type 1 diabetes. We also provide a comprehensive review of the putative mechanisms involved in these associations and their consequences for the management of affected women.

RESEARCH DESIGN AND METHODS

We followed the recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Guidelines (17).

Data Sources and Searches

We searched the Entrez-PubMed and Scopus online databases, introducing as Medical Subject Heading terms (diabetes mellitus, type 1 OR type 1 diabetes) AND (androgen excess OR hyperandrogenism OR polycystic ovary syndrome OR polycystic ovarian syndrome OR polycystic ovarian disease OR polycystic ovaries OR hirsutism OR acne OR alopecia OR menstrual dysfunction OR anovulation OR infertility OR subfertility OR ovulation induction).

Study Selection

Human studies published between 1966 and October 2015 written in English (or including an abstract in English) were considered further. The reference lists of the articles selected were also hand checked to identify studies missing in the primary search. There were no study format restrictions. Outcomes were prevalences of PCOS, hirsutism, hyperandrogenemia, menstrual dysfunction, and/or polycystic ovarian morphology (PCOM) in adolescent or adult women with type 1 diabetes. We selected articles containing at least one of the outcomes.

Data Extraction and Quality Assessment

Both authors screened titles and abstracts of all the articles and extracted data from those reporting frequencies of PCOS and related traits in adolescent and adult women with type 1 diabetes, provided that their diagnosis was based on locally (18) or internationally (19–21) accepted definitions. Valid international definitions included 1990 National Institutes of Health (NIH) (19), 2004 European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) (20), and 2006 Androgen Excess and PCOS Society (AE-PCOS) (21) criteria. In brief, all of the international definitions require the exclusion of specific etiologies such as nonclassic congenital adrenal hyperplasia, hyperprolactinemia, hypercortisolism, or androgen-secreting tumors. The NIH definition requires the presence of menstrual/ovulatory dysfunction together with clinical and/or biochemical hyperandrogenism (19). The ESHRE/ASRM and AE-PCOS definitions add PCOM as a criterion (20,21). The ESHRE/ASRM definition sustains a diagnosis of PCOS when two of the three criteria are present (20), whereas the AE-PCOS definition requires the presence of hyperandrogenism together with evidence of ovarian dysfunction, as indicated by ovulatory dysfunction and/or PCOM (21). Hence, the spectrum of disorders included by currently valid definitions of PCOS is variable, with NIH criteria being more and ESHRE/ASRM criteria being less restrictive. In fact, the latter may sustain a diagnosis of PCOS even in the absence of androgen excess such as in women presenting solely with ovulatory dysfunction and PCOM (20). The possible phenotypes meeting the criteria for PCOS according to the different international definitions are summarized in Table 1. In general, the presence of androgen excess associates with a more severe cardiometabolic phenotype in patients with PCOS (3).

For the present meta-analysis, in case the articles reported the prevalence of PCOS according to more than one valid definition of PCOS, we chose the definition that resulted in the largest prevalence estimate. We contacted the corresponding authors as needed to expand information that was unclear or not available in the original articles. The quality of the original studies was assessed by applying the *Q* index, which scores six quality scale variables (Supplementary Table 1) (22). The scores are then converted into quality ranks between 0 and 1 by dividing each score by the score of the highest scoring study in the group. The *Q* index was used to help reduce estimator variance by modeling redistribution of weights in the meta-analysis of prevalences (22).

Table 1—Possible phenotypes of PCOS according to the presence or absence of hirsutism, hyperandrogenemia, ovulatory dysfunction, and PCOM

	Potential phenotypes									
Features	A	B	C	D	E	F	G	H	I	J
Hyperandrogenemia	+	+	+	+	–	–	+	–	+	–
Clinical hyperandrogenism	+	+	–	–	+	+	+	+	–	–
Ovulatory dysfunction	+	+	+	+	+	+	–	–	–	+
PCOM	+	–	+	–	+	–	+	+	+	+
NIH definition (19)	√	√	√	√	√	√				
ESHRE/ASRM definition (20)	√	√	√	√	√	√	√	√	√	√
AE-PCOS definition (21)	√	√	√	√	√	√	√	√	√	

Modified from Azziz et al. (21), with permission (The Endocrine Society, Copyright 2006).

Data Synthesis and Analysis

Data regarding the prevalences of PCOS, hyperandrogenemia, hirsutism, menstrual dysfunction, and PCOM were meta-analyzed to obtain pooled prevalence estimates in women with type 1 diabetes. Because of the heterogeneous nature of the studies in age, race, ethnicity, criteria for the definition of PCOS and PCOM, and androgen assays used to estimate hyperandrogenemia, we used the quality-effects model for the meta-analysis (22). The quality-effects model relies on the use of the *Q* index to weight the studies and is more robust than fixed- or random-effects models when analyzing heterogeneous studies (22). We used MetaXL software (http://www.epigear.com/index_files/metaxl.html) for the meta-analyses. Double arcsine transformations were applied to stabilize the variance (22). Forest plots showed the pooled prevalence estimates as diamonds, with their lateral points indicating CIs. The left-hand column included study identifiers, and the right-hand columns included plots of the prevalences found in each of these studies (squares and horizontal lines representing CIs) and their corresponding numerical information. Publication bias was assessed by funnel plots representing the double arcsine transformation of the prevalence against the standard error (23).

RESULTS

Meta-analysis of Prevalence of PCOS and Related Traits

Figure 1 shows the MOOSE Guidelines flowchart, from identification of studies to meta-analysis. After duplicates were deleted, the initial search yielded 455 articles. Of them, 396 were subsequently excluded as unrelated to the scope of the systematic review, leaving 59 articles pertaining to reproductive issues in type 1 diabetes in women, including fertility, menstrual cycle, and traits related to androgen excess (Supplementary Data). Eighteen articles were reviews and/or case reports and were excluded (Supplementary Data). Six addressed fertility issues and eighteen addressed menstrual cycle characteristics of type 1 diabetes but were unrelated to androgen excess (Fig. 1 and Supplementary Data), leaving seventeen original articles dealing with androgen excess (8–16,24–31). Only 9 of these 17 articles contained data about the prevalence of PCOS and related traits (8,10–16,28) and were included in the meta-analyses. Table 2 summarizes the characteristics of these studies, and Supplementary Table 1 reports their *Q* indexes.

A total of 475 adolescent and adult women were included in the meta-analyses of the prevalences of PCOS and associated traits. Not all studies reported all of the outcomes; hence, the total numbers of women included in each meta-analysis are included in Fig. 2, which also shows forest and funnel plots for each analysis. The symmetry in the funnel plots ruled out substantial publication bias.

The pooled prevalence of PCOS in women with type 1 diabetes was 24% (95% CI 15–34) (Table 2 and Fig. 2). The smallest prevalence (7%) was found in Italian adolescents (13), and the largest (41%) was reported in Chilean adolescent and adult women (10) using the ESHRE/ASRM definition of PCOS (Table 2). In studies specifically reporting the prevalence according to different definitions of the syndrome (10,15), the largest prevalences were found when using the ESHRE/ASRM definition, followed by AE-PCOS and NIH criteria (Table 2).

Regarding the prevalences of androgen excess-related traits in women with type 1 diabetes, hyperandrogenemia was present in 25% (95% CI 17–33) of these women, hirsutism in 25% (95% CI 16–36), menstrual dysfunction in 24% (95% CI 17–32), and PCOM in 33% (95% CI 24–44) (Fig. 2 and Table 2).

Systematic Review

Characteristics and Severity of the PCOS Phenotype in Women With Type 1 Diabetes

The systematic review identified several articles that compared the PCOS phenotype in women with type 1 diabetes with that of women without diabetes (9,15,26,28,31). In several studies, the mean hirsutism score was lower in women with type 1 diabetes and PCOS than in their counterparts without diabetes (9,15,31), whereas no differences were found in others (16,26,28). The hormonal profiles of patients with PCOS, with or without type 1 diabetes, were comparable in circulating total testosterone concentrations in most studies (9,15,16,26), yet the cause of the increased free testosterone or free androgen index in patients with PCOS appears to derive from specific mechanisms in women with type 1 diabetes (15). In women with type 1 diabetes and PCOS, sex hormone–binding globulin (SHBG) concentrations are comparable to those of non-PCOS women with type 1 diabetes (9,16,26,28) or healthy control subjects (9,13,26) instead of being reduced as occurs in most women with PCOS but without diabetes (9,26,32). Hence, an increased total testosterone concentration, as opposed to decreased SHBG levels, appears to be the most important contributor to the increase in circulating free androgens in women with type 1 diabetes (9,15). Similarly, the increase in the follicle counts and in antimüllerian hormone concentrations (a circulating surrogate index of follicle counts) is milder in women with type 1 diabetes and PCOS compared with their counterparts without diabetes (26).

Several articles addressed the role of the ovary and the adrenal gland as sources of androgen excess in women with type 1 diabetes. Evaluation of adrenal function after stimulation with intravenous cosyntropin stimulation, together with normal circulating concentrations of the adrenal androgen dehydroepiandrosterone

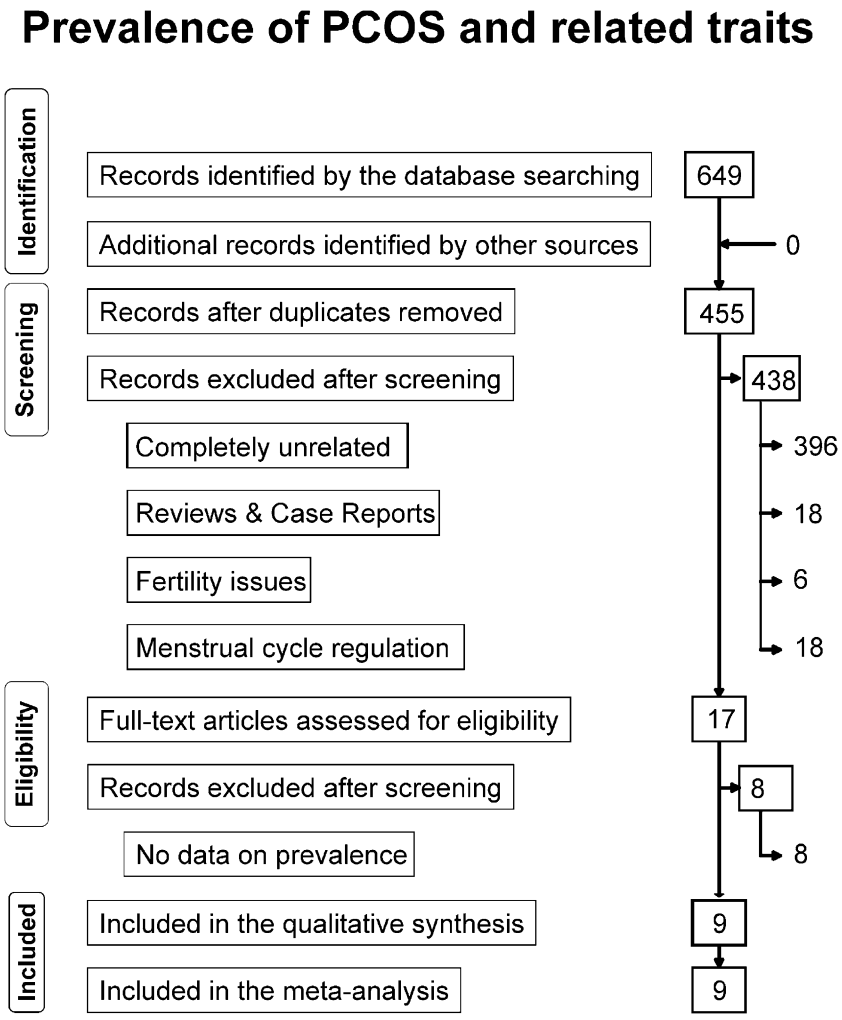

Figure 1—MOOSE Guidelines flowchart.

sulfate, initially suggested that the ovary was the most likely source of androgen excess in these women (9). This was also supported by the finding of androgenized ovarian responses to the gonadotropin-releasing hormone analog leuprolide in these women, consisting of increased circulating 17-hydroxyprogesterone concentrations (24,25). However, as happens in women without diabetes, the adrenal glands may also contribute to androgen excess in women with PCOS and type 1 diabetes, explaining the mildly increased dehydroepiandrosterone sulfate levels found in some series (14,28).

Differences in Women With Type 1 Diabetes Depending on the Presence or Absence of PCOS

Exogenous systemic hyperinsulinism may be involved in the pathogenesis of PCOS in women with type 1 diabetes. Therefore, the possibility exists that differences in the treatment of type 1 diabetes, such as glycemic control, daily insulin dose, and method of insulin administration, influence the association between both disorders.

Glycemic control and daily insulin doses at recruitment were similar in patients with type 1 diabetes presenting with or without PCOS or hyperandrogenic traits in most series (8,10,14–16,28), and only in one study was the insulin dose higher in patients with type 1 diabetes with PCOS (11). Another study reported slightly higher mean HbA_{1c} levels since diagnosis of type 1 diabetes in the patients presenting with PCOS and an association between androgen concentrations and mean HbA_{1c} and type 1 diabetes duration in adolescents with poor metabolic control (15).

The comparison between conventional (less than three doses of insulin per day) and intensive insulin treatment (multiple dose injection or continuous subcutaneous insulin infusion) was only possible in the study conducted in Chile because at that time intensive insulin treatment was not covered by the Chilean health system (10). Women under intensive insulin treatment had a significantly higher prevalence of PCOM and PCOS compared with those under conventional two-dose insulin treatment (10). Three studies included patients on intensive treatment with multiple dose injection or continuous subcutaneous insulin infusion, and no differences were observed in the appearance of PCOS or hyperandrogenic symptoms (13,15,16).

Considering that androgen excess disorders and traits usually have a peripubertal onset in the general population, the timing of the onset of type 1 diabetes and its duration might influence the association with hyperandrogenism. Duration of type 1 diabetes was longer in hirsute patients with type 1 diabetes compared with their nonhirsute counterparts in French adolescents (28). The gynecological age of women with type 1 diabetes and PCOS was younger in one study (15). Moreover, a more frequent premenarcheal onset of type 1 diabetes in patients with androgen excess traits (PCOS or hirsutism) was close to reaching statistical significance in women from Spain (8), and menarche tended to be earlier in PCOS patients with type 1 diabetes from Italy (16). However, no differences in these and other variables, such as age at the onset of diabetes or personal history of premature pubarche, were reported in other studies (8,10,15,16).

Even though we hypothesized that exogenous systemic hyperinsulinism may play a major role in the development of androgen excess in women with type 1 diabetes, the fact that most women with type 1 diabetes do not show any evidence of hyperandrogenic traits suggests that a certain individual predisposition toward the development of androgen excess is also required for PCOS to develop.

In conceptual agreement, a positive family history of hirsutism, acne, menstrual dysfunction, hyperandrogenemia, and PCOM was more frequent in women with type 1 diabetes and PCOS compared with those without androgen excess traits in the largest series published

to date (16), suggesting that an inherited component is part of this predisposition. Unfortunately, no data are available about genetic variants associated with PCOS in the general population in the subset of women with type 1 diabetes and androgen excess.

In another study, hirsute girls with type 1 diabetes tended to have more frequently a positive family history of type 2 diabetes and obesity compared with girls with type 1 diabetes but no hirsutism (28). These girls with type 1 diabetes and hirsutism had a larger waist circumference than those without hirsutism, despite similar BMI values (28). Moreover, some women with type 1 diabetes and PCOS had an increased visceral adiposity index and circulating triglycerides concentrations compared with their nonhyperandrogenic counterparts (16), and their mean waist-to-hip ratio was increased compared with that of the healthy population but to a lesser extent compared with girls without diabetes with PCOS (26). Furthermore, adolescence in women with type 1 diabetes is characterized by a decrease in the insulin-sensitizing adipokine adiponectin, and its decrease correlates with increasing serum testosterone concentrations and ovarian volume (27), as also happens in women with PCOS without type 1 diabetes (33).

Taken together, these findings suggest that PCOS in type 1 diabetes may be influenced to some extent by the same metabolic associations, related to insulin resistance, that are frequently found in patients with PCOS without type 1 diabetes from the general population (4). However, treatment with the insulin-sensitizer drug metformin for 9 months in hyperandrogenic women with type 1 diabetes, although effective in lowering serum androgen concentrations, did not result in any improvement of hyperandrogenic symptoms or metabolic control, indicating that insulin resistance is apparently not the major contributor to androgen excess in these women (29). Anyhow, it must be noted that BMI was not different among women with type 1 diabetes, with or without hyperandrogenic disorders, in the studies reviewed here (8,10,14–16,28).

CONCLUSIONS

Our present meta-analysis shows that PCOS is present in almost one of every

Table 2—Summary data of the observational studies submitted to meta-analyses of the pooled prevalences of PCOS, hyperandrogenemia, hirsutism, menstrual dysfunction, and PCOM in women with type 1 diabetes

First author (reference)	Country	Patients (*n*)	Ethnicity	Age (years)	BMI (kg/m^2)	Criteria for PCOS			Hyperandrogenemia (%)	Hirsutism (%)	Menstrual dysfunction (%)	PCOM (%)
						NIH (%)	ESHRE/ASRM (%)	AE-PCOS (%)				
Escobar-Morreale (8)	Spain	85	Caucasian	22 ± 5	23 ± 3	19	NR	NR	19	38	19	NR
Codner (10)	Chile	42	Mixed	23 ± 1	25 ± 1	12	41	36	24	29	17	55
Miulescu (11)	Romania	24	NR	NR	NR	NR	17	NR	NR	58	NR	21
Kvasničková (12)	Czech Republic	21	Caucasian	33 ± 7	24 ± 4	NR	24	NR	38	5	19	24
Bizzarri (13)	Italy	54	Caucasian	17 ± 2	24 ± 4	7	7	7	19	26	11	24
Samara-Boustani (28)†	France	78	Mixed	14 ± 2	0.8 ± 1.0*	NR	NR	NR	NR	21	44	NR
Miyoshi (14)‡	Japan	21	Asian	34 ± 6	22 ± 3	NR	NR	NR	NR	NR	24	52
Zachurzok (15)	Poland	47	Caucasian	16 ± 1	0.4 ± 0.3*	2	26	19	45	6	34	38
Amato (16)	Italy	103	Caucasian	27 ± 6	22 ± 3	32	37	37	22	27	28	29

Data are means ± SD or as indicated. NR, not reported. *These values are z-scores. †The prevalence of PCOS was not described, and data presentation did not permit its calculation. ‡This study reported Japanese criteria of PCOS: PCOM in addition to increased luteinizing hormone concentrations and/or hyperandrogenemia.

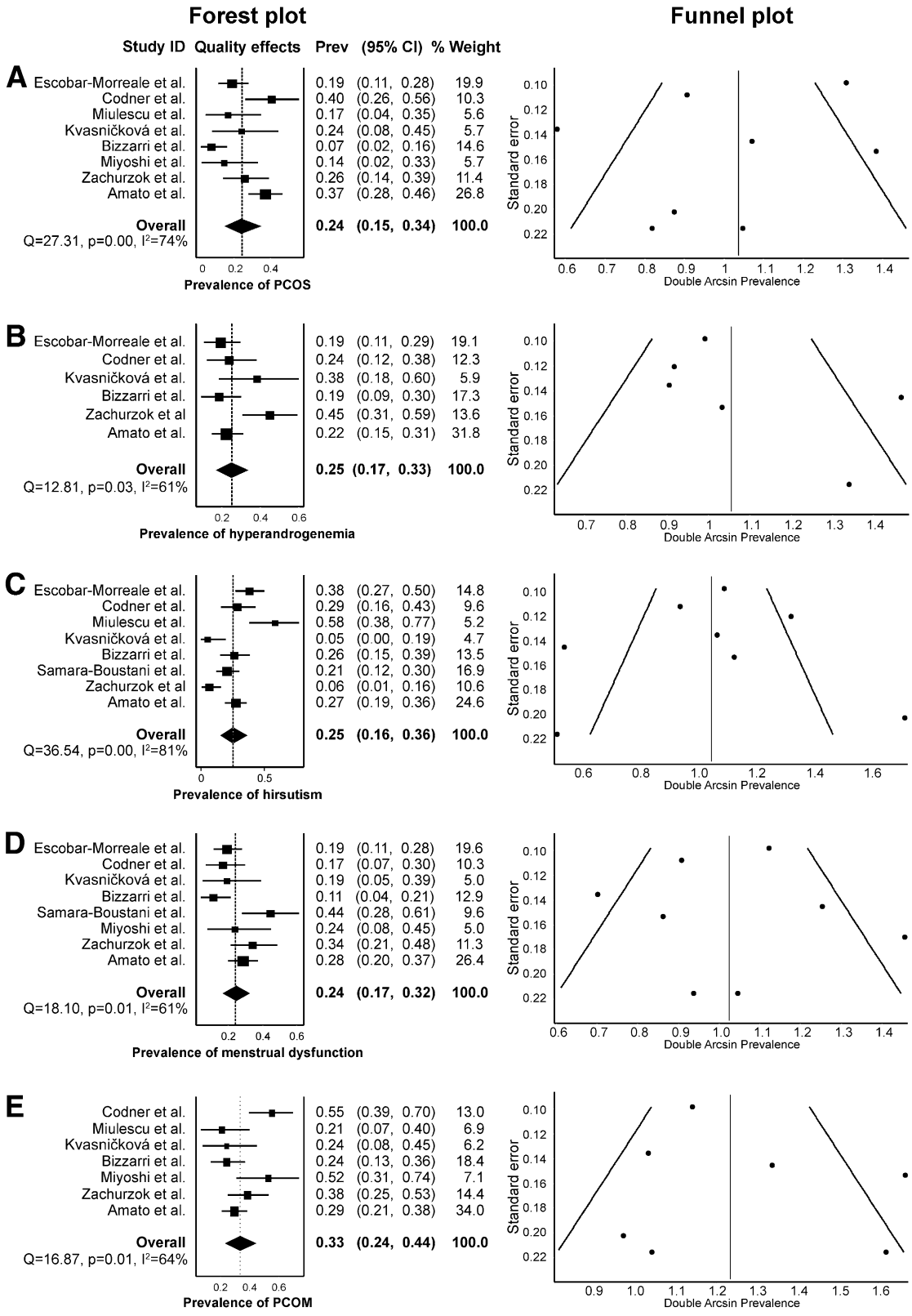

Figure 2—Meta-analysis (quality-effects model) of the pooled prevalence (Prev) of PCOS (*A*), hyperandrogenemia (*B*), hirsutism (*C*), menstrual dysfunction (*D*), and PCOM (*E*) in women with type 1 diabetes, including forest and funnel plots.

four women with type 1 diabetes, possibly making this syndrome the most frequent—and commonly missed—comorbidity in these women. The prevalence of PCOS varied among studies, depending on the reference population, the age of the patients, and the diagnostic criteria used for the diagnosis of PCOS. Being more restrictive, studies that applied NIH criteria resulted in lower prevalences of PCOS (8,10) compared with those observed in studies

that applied AE-PCOS (10,15,16) or ESHRE/ASRM (10–13,15) definitions. The same occurred within the studies that calculated the prevalence of PCOS according to the three valid international definitions of the syndrome in single series of women with type 1 diabetes (10,15). Moreover, the lowest prevalence was found in the study conducted in very young women, and the possibility exists that some of these girls with diabetes would have needed more time to develop the full PCOS phenotype (13).

Irrespective of these considerations, the pooled 24% (95% CI 15–34) prevalence of PCOS in adolescent and adult women with type 1 diabetes is markedly increased compared with the prevalence reported in the general population. Such figures vary from ~4 to 8% when applying NIH criteria (1,34–42) to 7 to 15% when using AE-PCOS criteria (38,39,42) and to 6 to 20% when using ESHRE/ASRM criteria (39,42–44). In contrast, the prevalence of PCOS in women with type 1 diabetes may reach figures as high as 19% when applying NIH criteria (8), 37% when using AE-PCOS definition (16), and 41% when applying ESHRE/ASRM criteria (10).

However, race and ethnicity might influence the prevalence of PCOS in the general population, with figures as low as 2.4% in Southern China or as high as 21% in Australian Indigenous women (42) according to ESHRE/ASRM criteria. When taking into account these considerations, data obtained in specific countries where the prevalence of PCOS in the general population is known, such as Spain and Italy (1,41), still indicate that PCOS is much more frequent in women with type 1 diabetes (8,13,16).

The prevalence of androgen excess traits, particularly hirsutism, was also very high in women with type 1 diabetes. The 25% (95% CI 15–36) pooled prevalence of hirsutism is clearly increased when compared with the figures found in the general population (45). The prevalence of hirsutism in Caucasian women, such as the hirsute women with type 1 diabetes included in the meta-analysis, varies within the 5–11% range (1,40,42,46–48), because the much higher prevalence of hirsutism reported in two studies (35,39) might have resulted from possible selection self-referred bias (45). Similarly, the 25% (95% CI 17–33) pooled prevalence of hyperandrogenemia is clearly elevated, because we should assume that the reference values for circulating androgen concentrations were appropriately set for each of the original studies and, accordingly, should be close to the 95th percentile of the women in the general population of each city or country.

Comparing the 24% (95% CI 17–32) prevalence of menstrual and/or ovulatory dysfunction in women with type 1 diabetes with those in the general population is much more difficult because data from the general population are surprisingly scarce. The prevalence of oligomenorrhea and amenorrhea in a very large series of American female college students was 11.3% and 2.6%, respectively (49), but because the prevalence of PCOS in the general population is large, some of these women might have had PCOS. Considering that the prevalence of isolated oligomenorrhea (after excluding signs and symptoms of androgen excess) in blood donors from Spain and Italy was 4.2% (95% CI 2.6–5.8) (41), we may conclude that the prevalence of firmly established menstrual dysfunction in women with type 1 diabetes is increased with respect to healthy women. Yet it must be noted that menstrual dysfunction in type 1 diabetes results not only from androgen excess but also from abnormalities in gonadotropin secretion (50) in association with complications of diabetes, poor metabolic control, or weight gain (51).

The 33% (95% CI 34–44) prevalence of PCOM in women with type 1 diabetes was also very high. Of note, all of the studies included in the meta-analysis used ultrasound equipment with maximum transducer frequencies below 8 MHz and appropriately relied on ESHRE/ASRM criteria for the definition of PCOM: ovarian volume above 10 mL and/or 12 or more follicles measuring 2–9 mm in diameter in at least one ovary (20). Even though the pooled prevalence of PCOM in women with type 1 diabetes might not appear too high if compared with the prevalences reported by recent studies (52,53) in regularly menstruating women showing no evidence of androgen excess—the threshold of 12 follicles per ovary was met by almost 50% of them—it must be highlighted that these studies used modern ultrasound machines equipped with maximum transducer frequencies above 8 MHz. The markedly improved spatial resolution of this ultrasound equipment permits the detection of small ovarian follicles that were missed by older machines, thereby invalidating any comparison between the prevalences of PCOM in women with type 1 diabetes reported earlier and recent estimates in apparently healthy women. In this regard, the AE-PCOS Society guidelines currently recommend increasing the cutoff value to 25 follicles per ovary when modern ultrasound equipment is used because this figure corresponds to the 95th percentile observed in large series of apparently healthy women (53). To our best knowledge, these recently updated PCOM criteria have not been applied to the study of women with type 1 diabetes to date, and anyway, these considerations would not affect the large incidence of hyperandrogenic phenotypes found in women with type 1 diabetes.

Albeit the meta-analysis conducted here demonstrates that PCOS and related traits are more prevalent in women with type 1 diabetes than in women from the general population, the systematic review was less useful in exploring the mechanisms leading to androgen excess in type 1 diabetes and the clinical consequences of this association.

The androgen profiles of patients with PCOS and type 1 diabetes are similar to those of patients without type 1 diabetes, with the exception of normal SHBG concentrations and a less pronounced increase in free testosterone concentrations and/or the free androgen index (9,15,26). Only in one study (16) were SHBG levels similar in patients with PCOS with or without type 1 diabetes. However, the mean concentrations of SHBG in both groups of patients with PCOS were very high (101 nmol/L in women with type 1 diabetes and PCOS and 91 nmol/L in their counterparts without diabetes) and close to the upper limit of the normal range (114 nmol/L) for the immunochemiluminescent assay used in this study (16). Such very high SHBG levels are found rarely in patients with PCOS from the general population, in whom SHBG concentrations are usually in the 20 to 50 nmol/L range (54).

The reduced secretion of SHBG in patients with PCOS is believed to result

from the combined inhibitory influence of portal insulin levels (55), proinflammatory mediators mostly secreted by liver adipose tissue (56), and excessive circulating androgens (57) in association with insulin resistance, visceral adiposity, and hyperandrogenism. However, the lack of reduced SHBG concentrations in women with type 1 diabetes and PCOS may suggest that the major pathogenetic mechanism is related to the subcutaneous route of administration of insulin (58).

Subcutaneous insulin administration results in hyperinsulinism in the systemic circulation in order to reach the normal portal insulin concentrations needed to suppress hepatic glucose output. Accordingly, the ovary and possibly the adrenals are necessarily exposed to excessive insulin concentrations and may lead to androgen excess in predisposed women (4), as may occur in response to endogenous compensatory hyperinsulinism in insulin-resistant women not receiving insulin (3). However, definitive proof of the involvement of this mechanism would require the development and wide use of methods that administer exogenous insulin directly into the portal circulation in patients with type 1 diabetes.

Insulin resistance might also influence the association of type 1 diabetes with PCOS, especially in women with a family history of obesity (28) or data suggestive of visceral adiposity (16), but the lack of improvement of signs and symptoms in response to the administration of metformin (29) indicates that its role, if any, is minor.

Moreover, the normal circulating SHBG concentrations, by decreasing the amount of bioavailable and free testosterone, might explain why the hyperandrogenic phenotype of patients with PCOS may be milder in women with type 1 diabetes compared with patients with PCOS but without diabetes despite similarly increased total testosterone concentrations (9,15,31). Also, serum testosterone concentrations may improve in patients with type 1 diabetes as they become older, similarly to what has been described in patients with PCOS but without diabetes (59). This milder phenotype, together with the fact that most medical efforts are usually focused on the adequate control of type 1 diabetes in order to avoid the long-term micro- and macrovascular complications of the disease, may contribute to explain why PCOS goes unrecognized in most women with type 1 diabetes nowadays.

Unfortunately, the clinical consequences of the association of type 1 diabetes and PCOS remain largely unknown because no long-term follow-up studies have been conducted to date. In our clinical experience, skin manifestations of androgen excess, such as hirsutism or acne, and menstrual disturbances are controlled satisfactorily with oral contraceptive pills, without any relevant effect for the management of diabetes. But other possible consequences of PCOS for fertility or pregnancy, for endometrial health, or even the possible development of metabolic derangements, have not been studied to date in women with type 1 diabetes. Importantly, the increasing prevalence of obesity and metabolic syndrome in type 1 diabetes has occurred in recent years and might influence the association with PCOS.

In fact, type 1 diabetes is associated with subfertility (60), decreased sexual function, and increased sexual distress (61). Even though the current explanation is that these findings are related to poor glycemic control of type 1 diabetes (60), it must be noted that patients without diabetes with PCOS suffer from the same fertility and sexual function issues (62). For example, a normal ovulation rate has been found in women with type 1 diabetes without androgen excess (63). Therefore, at least in theory, the anovulation characteristic of PCOS, and not type 1 diabetes per se, may contribute to the decreased fecundability reported in these women (64). Definitely, studies addressing the role of PCOS in the fertility and sexual functioning of type 1 diabetes are urgently needed. If these issues were actually related to androgen excess and not to poor metabolic control, their management would be radically different and would require specific approaches such as ovulation induction or assisted reproductive techniques and amelioration of androgen excess.

As stated above, the aim of the present work was to increase awareness of the frequent association of PCOS with type 1 diabetes. To date, screening for PCOS is not recommended, to our knowledge, by any local or international clinical guideline for the management of women with type 1 diabetes, despite the large percentage of these women affected with the syndrome and the potential negative consequences for their reproductive and sexual health.

Furthermore, only by increasing awareness of the association and by conducting large and properly designed scientific studies will many of the unresolved issues be answered. Future venues of research should prioritize:

1. Conducting large multicenter studies addressing the prevalence of PCOS and other traits related to androgen excess in women with type 1 diabetes and in women from the general population matched for age, race, ethnicity, and socioeconomic background.
2. Comparing the androgen excess phenotype of women with type 1 diabetes with that of women without diabetes in large series of patients. The populations without diabetes should include patients with PCOS identified from the general population and patients identified at the clinical setting, because referral bias may influence the hyperandrogenic and metabolic phenotype of these women (65).
3. Identifying the pathophysiological mechanisms underlying PCOS in women with type 1 diabetes by careful comparison with women with diabetes who do not develop the syndrome. This aim would require clinical and translational studies using targeted and nontargeted molecular genetic techniques and state-of-the-art genomic, proteomic, metabolomic, and epigenetic methods.
4. Addressing the long-term consequences of PCOS in women with type 1 diabetes in large multicenter prospective studies focused on reproductive and sexual function.
5. Addressing in large multicenter randomized trials the specific effects of drugs currently in use for PCOS in the subpopulation with type 1 diabetes, including oral contraceptives, antiandrogens, insulin sensitizers, and drugs used for ovulation induction.
6. Developing future methods of insulin administration directly into the portal circulation. Ideally, these methods should also measure glycemia in

hepatic portal effluents. Relying on the portal circulation for glucose measurements and insulin administration will facilitate the development of accurate algorithms to be used in closed-loop systems, leading to a reduction in the insulin doses needed to control type 1 diabetes, thereby avoiding systemic hyperinsulinism in these patients.

Conclusion

Despite the limited evidence available to date, PCOS and related hyperandrogenic traits appear to be among the most common comorbidities of type 1 diabetes in premenopausal women, with prevalences in the 24 to 33% range. The mechanisms underlying this association remain largely unknown, yet the possibility exists that exogenous hyperinsulinism, resulting from the administration of large doses of insulin through the nonphysiological subcutaneous route, plays a major role triggering an intrinsic predisposition to secrete increased amounts of androgens. Similarly, the long-term consequences of PCOS for women with type 1 diabetes remain unclear. Nevertheless, considering that PCOS has substantial negative consequences for the health of women and that this syndrome may be present in as many as one in every four women with type 1 diabetes, the routine screening for PCOS and related traits in these women seems warranted. Only the inclusion of routine screening of PCOS in current guidelines for the management of type 1 diabetes in women would permit substantial advancements in our knowledge about this frequent association and the development of evidence-based recommendations for its management.

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