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Investigation of metabolic parameters of women of reproductive age

Doğurganlık çağındaki kadınlarda metabolik parametrelerinin incelenmesi

Aslıhan Mete Yıldırım[1], Funda Datlı Yakaryılmaz[2]

[1]İnönü University, Faculty of Medicine, Department of Medical Education, Malatya, Türkiye
[2]İnönü University, Faculty of Medicine, Department of Internal Medicine, Geriatrics, Malatya, Türkiye

ABSTRACT

***Aim*:** Fertility rates are decreasing every year, mainly due to socioeconomic and medical reasons. In this study it was aimed to investigate the incidence of metabolic disorders that may negatively affect reproduction.
Methods: Glucose parameters of 5892 patients, lipid parameters of 2491 patients and thyroid function tests of 457 patients were retrospectively examined. Patients divided into two groups in terms of age. Each age groups were divided into subgroups as diabetic, prediabetic, non-diabetic and euthyroidism, overt hypothyroidism, subclinical hypothyroidism and hyperthyroidism.
Results*:* The rate of euthyroidism was 85.8%, overt hypothyroidism was 4.2%, subclinical hypothyroidism was 3.5%, and hyperthyroidism (subclinical+overt) was 6.5% in all ages. There was no significant difference in ft3, ft4 and TSH values according to age (p values 0.051; 0.195; 0.585, respectively). The rate of diabetes was 4.7%, non-diabetes 83.7% and prediabetes was 11.6%. There was a significant difference between diabetic, prediabetic, and non-diabetic according to age (p<0.001). There was a significant difference in Total Cholesterol, LDL, HDL and Triglyceride values between diabetic, prediabetic and non-diabetic patients (p values 0.021; <0.001; 0.034; <0.001, respectively).
Conclusion: Thyroid dysfunction and glucose metabolism disorders are more common in the women of Türkiye due to genetic and environmental factors. Early diagnosis is very important to avoid the unwilling side effects of this condition. For this, new approaches are needed, such as close follow-up clinics aimed only at women of reproductive age.

Keywords*:* fertility; metabolic; women

ÖZ

Amaç: Doğurganlık oranları, başta sosyoekonomik ve tıbbi nedenler olmak üzere her yıl azalmaktadır. Bu çalışmada doğurganlığı olumsuz etkileyebilecek metabolik bozuklukların görülme sıklığı araştırılması amaçlandı.
Yöntem: 5892 hastanın glukoz parametreleri, 2491 hastanın lipit parametreleri ve 457 hastanın tiroid fonksiyon testleri retrospektif olarak incelendi. Hastalar yaşlarına göre iki gruba ayrıldı. Her yaş grubu diyabetik, prediyabetik, diyabetik olmayan ve ötiroidizm, aşikar hipotiroidizm, subklinik hipotiroidizm ve hipertiroidizm olarak alt gruplara ayrıldı.
Bulgular: Tüm yaş gruplarında ötiroidizm oranı %85.8, aşikar hipotiroidizm %4.2, subklinik hipotiroidizm %3.5 ve hipertiroidizm (subklinik+aşikar) %6.5 olarak tespit edildi. Yaşa göre ft3, ft4 ve TSH değerlerinde anlamlı farklılık yoktu (sırasıyla p değerleri p=0.051, p=0.195, p=0.585). Diyabetlilerin oranı %4.7, diyabetik olmayanların oranı % 83.7, prediyabetlilerin oranı ise % 11.6 oldu. Yaşa göre diyabetik, prediyabetik ve diyabetik olmayanlar arasında anlamlı fark vardı (p<0.001). Diyabetik, prediyabetik ve diyabeti olmayan hastalar arasında Total Kolesterol, LDL, HDL ve Trigliserid değerleri arasında anlamlı fark mevcuttu (p değerleri sırasıyla 0.021; <0.001; 0.034; <0.001).
Sonuçlar: Türkiye'deki kadınlarda genetik ve çevresel faktörlere bağlı olarak tiroid fonksiyon bozuklukları ve glukoz metabolizma bozuklukları daha sık görülmektedir. Bu durumun istenmeyen yan etkilerinden kaçınmak için erken teşhis çok önemlidir. Bunun için sadece üreme çağındaki kadınlara yönelik yakın takip klinikleri gibi yeni yaklaşımlara ihtiyaç vardır.

Anahtar kelimeler*:* fertilite; kadın; metabolik

Introduction

Fertility rates are decreasing every passing day especially in the developed and developing countries. According to the data from Turkish Statistical Institute, feritlity rate was decreased to 1.51 in 2023 which was 1.62 in 2022. This ratio is predicted to be decreased in 2024 (Türkiye İstatistik Kurumu, 2024). The decline in the fertility rate is a problem that needs to be addressed not only because it will cause the aging of society but also because it will lead to a change in demographic characteristics. As well as economic, socio-demographic and cultural effects on the decline in fertility, there are also various medical reasons. In addition to the social policies that need to be implemented in this regard, some medical measures should also be taken. It is also a fact that scientists, as well as states, must work actively in this regard. In this study it was aimed to investigate the rate of most common reasons of infertiliy in women.

Although there is no large-scale study investigating the prevalence of thyroid diseases in women of reproductive age, it is estimated to be between 2-17% (Demir, 2017; Çakır, 2004). Since Türkiye is in a moderately endemic iodine deficiency region, close follow-up is required for thyroid diseases (Demir, 2017). In addition, it is known that thyroid dysfunction causes a wide variety of menstrual disorders (Krassas et al., 2010). There are many studies linking thyroid diseases with infertility and early pregnancy complications (Kirkegaard et al., 2024). In addition to causing morbidities in babies and pregnant women, thyroid dysfunction is important because it is one of the most important causes of treatable infertility.

Diabetes and prediabetes diseases, which have negative

Corresponding Author: Aslıhan Mete Yıldırım, İnönü University, Faculty of Medicine, Department of Medical Education, Malatya, Türkiye
Phone: +90 505 914 2240, E-mail: aslihanmy@gmail.com
Received: 11.06.2024, Accepted: 06.08.2024
ORCID: Aslıhan Mete Yıldırım: 0000-0001-7482-4596, Funda Datlı Yakaryılmaz: 0000-0001-5633-0939

effects on fertility, are important because they are common in our country. According to a recent large-scale study, the rate of diabetes among women in Türkiye is 14.6%, and the rate of diabetes between the ages of 20-44 is 6.5%. (Satman et al., 2013). Diabetes is an important disease in terms of causing ovulatory disorders in women in the reproductive period, pregnancy losses and morbidities for mother and baby. Reproductive effects of insulin resistance and diabetes include irregular menstrual cycles, anovulatory infertility, increased pregnancy complications (Stener-Victorin et al., 2024). Prediabetes is also requires attention because it remains hidden, its diagnosis is overlooked, and it has negative effects on fertility.

In the study it was aimed to investigate the thyroid hormone and blood sugar levels of female patients between the ages of 18-49, where fertility is highest, and to determine the rates of disorders in these metabolisms.

Methods

Study population

After ethics committee approval was obtained, female outpatients aged 18-49 years who applied to İnönü University Faculty of Medicine Turgut Özal Medical Center Internal Medicine Outpatient Clinic between 2019-2021 were retrospectively screened.

In evaluating thyroid functions, 457 with TSH, 415 patients with ft4 and 335 patients with ft3 patients were divided into 2 age groups, 20-29 and 30-49 years, based on the values in the Turkish Endocrinology and Metabolism Association (TEMD) Thyroid diseases guide (Türkiye Endokrinoloji ve Metabolizma Derneği, 2023).

Since the guide does not specify separate reference values for ages 18 and 19, the reference values for this age group were included in the 20-29 age group in the study. In examining lipid and glucose parameters, patients were divided into 2 age groups: 18-35 and 36-49 years. 5892 patients with glucose parameters and 2491 patients with lipid parameters were included in the study. Only women patients between 18-49 years were included in the study. Pregnant women and patients with missing data excluded the study.

Laboratory evaluation

Thyorid stimulating hormone (TSH), free t3 (ft3), free t4 (ft4), Fasting blood glucose (FBG), Total cholesterol (TC), low density lipoprotein (LDL), High density lipoprotein (HDL) and Triglyceride (TG) levels were obtained from venous blood after 8 hours fasting.

In accordance with the guide of the Turkish Endocrine and Metabolism Association, the upper TSH limit for the 20-29 age range was accepted as 3.5, and the TSH upper limit for the 30-49 age range was accepted as 4.5 (Türkiye Endokrinoloji ve Metabolizma Derneği, 2023).

In terms of thyroid dysfunction;

- Those with TSH ≥ 5 mIU/L and ft3 < 0.61 pg/mL and/or ft4 <2.3 ng/mL have overt hypothyroidism
- Those whose TSH is between 5-10 mIU/L while ft3 and ft4 are at normal levels have subclinical hypothyroidism
- Those with normal levels of ft3-ft4 and TSH are euthyroid
- Those with TSH <0.35 and ft3 > 4.2 pg/mL and/or ft4 > 4.2 ng/mL were grouped as hyperthyroidism
- The patients were divided into 3 groups: diabetic, non-diabetic and prediabetic.

According to this;

- Patients with FBG<100 mg/dl and HbA1c<5.7 and those without a previous diagnosis of diabetes are considered nondiabetic.
- Those who have FBG≥126 mg/dl and/or HbA1c≥6.5 are diabetic
- Patients with FBG 100-125 mg/dl and HbA1c 5.7-6.5 and patients who were not previously diagnosed with diabetes were grouped as prediabetic.

HbA1c measurements were made with a Chromsystem autoanalyzer (München, Germany) after 8 hours fasting. Results were reported in %. Total cholesterol, HDL cholesterol, LDL cholesterol and TG measurements were made with a Beckman Coulter UniCel DxI 800 (CA, USA) autoanalyzer after 8 hours fasting and reported in mg/dL

According to the TEMD guide for dyslipidemia optimal ranges of lipids were below

- Total-C<200 mg/dL
- LDL-C<100 mg/dL (<70 mg/dL for the patienst with high risk)
- HDL-C≥60 mg/dL
- TG<150 mg/dL

Statistical analysis

IBM SPSS 26.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA, 2019) was used for statistical analysis. Descriptive statistics were expressed mean ± standard deviation values. Additionally, categorical variables were presented as frequencies and percentages (%). Student t test was used to compare normally distributed data. Welch anova test was performed to compare 3 or more groups with non-normal distribution. Differences between groups in Welch ANOVA results were shown with post hoc Tamhane test. Statistical significance was defined as a probability (p) value of ≤ 0.05. Statistical significance for welch anova was defined as p value of ≤0.017

Ethical aspect of research

This study was approved by Inonu University Health Sciences Non-interventional Clinical Research Ethics Committee on 07/01/2024 with decision number: 2024/6032.

Results

The age of a total of 6775 patients included in the study was 23.18 ± 9.45 years. fT3, fT4, TSH, TC, LDL, HDL, TG, FBG and HbA1c values of the patients are shown in Table 1.

The mean ft3, ft4 and TSH values of the patients and their differences according to age groups are given in Table 2. Accordingly, there is no significant difference in ft3, ft4 and TSH values according to age (p values p = 0.051, p = 0.195, p = 0.585, respectively).

Table 1. Laboratory values of patients

Variables	Mean ± SD
Fasting Glucose (mg/dL)	92.62 ± 25.28
HbA1c (%)	5.7 ± 1.02
TC (mg/dL)	187.3 ± 46.30
LDL (mg/dL)	110.2 ± 37.53
HDL (mg/dL)	55.2 ± 12.35
TG (mg/dL)	109.4 ± 73.35
fT3 (pg/mL)	3.47 ± 1.01
fT4 (ng/mL)	1.19 ± 0.53
TSH (mIU/L)	2.59 ± 7.11

TC: Total Cholesterol; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglyceride; fT3: free triiodothyronine; fT4: free thyroxine; TSH: Thyroid Stimulating Hormone

Table 2. Differences between age groups in terms of ft3, ft4 and TSH

Variables	Groups	n	Mean±SD	p
fT3	18-29	137	3.61 ± 1.12	0.051
	30-49	198	3.38 ± 0.91	
fT4	18-29	171	1.23 ± 0.59	0.195
	30-49	244	1.16 ± 0.48	
TSH	18-29	192	2.83 ± 9.85	0.585
	30-49	265	2.42 ± 4.21	

fT3: free triiodothyronine; fT4: free thyroxine; TSH: Thyroid Stimulating Hormone

In the analysis of patients based on the upper limits of TSH determined in the guidelines, it was observed that the rate of those with TSH<3.5 mIU/L in patients aged 18-29 was 88.5%, and the rate of those with TSH<4.5 mIU/L in patients between the ages of 30-49 was 93.2%.

The rate of Euthyroidism was 85.8%, overt hypothyroidism was 4.2%, subclinical hypothyroidism was 3.5%, and hyperthyroidism (subclinical+overt) was 6.5% in all ages. When divided into age groups, euthyroidism was found to be 89.2%, overt hypothyroidism 3.0%, subclinical hypothyroidism 3.0%, and hyperthyroidism (subclinical+overt) 4.8% in the 18-29 age group. In the 30-49 age group, euthyroidism was 83.5%, overt hypothyroidism was 5.1%, subclinical hypothyroidism was 3.5%, and hyperthyroidism (subclinical+overt) was 7.6% (Table 3).

Table 3. Range of thyroid functions according to age

Variables	18-29 Ages (%)	30-49 Ages (%)	All Ages (%)
Euthyroidism	89.2	83.5	85.8
Overt Hypothyroidism	3.0	5.1	4.2
Subclinical Hypothyroidism	3.0	3.8	3.5
Hyperthyroidism (subclinical+overt)	4.8	7.6	6.5

According to the FBG and HbA1c levels, it was observed that the rate of diabetes was 4.7%, non-diabetes 83.7% and prediabetes was 11.6%. There was a significant difference between the groups in terms of fasting plasma glucose and HbA1c levels (p<0.001; p<0.001 respectively). The fasting plasma glucose, HBA1c and lipid parameters of diabetic, prediabetic and non-diabetic patients were given in Table 4.

When comparing the lipid parameters of diabetic and non-diabetic patients, it was observed that there was a significant difference in terms of TC, LDL, HDL, TG levels (p<0.001). Likewise when comparing non-diabetic patients with prediabetic patients, there was a significant difference in terms of TC, LDL, HDL, TG levels (p<0.001, p<0.001, p=0.003, p<0.001, respectively). When compared the lipid parameters of diabetic and prediabetic patients, there was a significant difference between HDL, TC and TG values. (p=0.015, p=0.023, p<0.001 respectively).

Discussion

In this study the average value of HbA1c levels was observed to be 5.7±1.02. This shows that the patients are at risk for prediabetes. In the literature the prevalence of prediabetes is given at higher rates than this studies finding. This may be due to the fact that there were younger patients in this study, or that only HbA1c and FBG levels were taken into account for prediabetes. According to the TURDEP II study it was reported that diabetes rate based on HbA1c levels was 3%. In this study this rate was 4.7%. Considering that there has been a 90% increase in the prevalence of diabetes in Türkiye in 12 years, the higher rates in this study suggested that it could also be an indicator of the increase in the prevalence of diabetes (Satman et al., 2013).

Another remarkable result in this study was that the average LDL levels were 110±37.52. It is a knowledge that, due to the effects of the estrogen hormone, women's risk of heart diseases is lower and their lipid profiles in the pre-menopausal period are within more normal limits than men (Morselli et al., 2017; Xiang et al., 2021). In a recent review study conducted in Türkiye, it was observed that the average LDL levels were at higher (Kızılırmak et al., 2020). This difference is probably due to the fact that the population in our study was premenopausal women. When dividing the patients into diabetic and prediabetic, it is seen that their lipid profiles are at risky levels. It has also been stated in the literature that dyslipidemia creates a predisposition to risky conditions such as preeclampsia and gestational hypertension (Hosier et al., 2023). For these reasons, monitoring lipid values in reproductive women may also be important.

In this study it was observed that there was difference between thyroid hormone levels according to the ages. When looking at the accepted upper limits of TSH levels in age groups, it was seen thar they were at acceptable levels at 88.5% in the 18-29 age group an 9.2% in the 30-49 age group. This finding suggest that although it is an endemic iodine deficiency region, the studies and public health programs carried out in terms of iodine replacement in Türkiye are benefical. In addition, checking thyroid functions of women considering pregnancy in our country when they apply to both family physicians and internal medicine and gynecology outpatient clinics enables the detection of any pathological course in advance (Halk Sağlığı Genel Müdürlüğü, 2019; Uğurlu & Aslan, 2023).

It was observed that in this study there was a higher rate of overt hypothyroidism than in literature (Atmaca, 2013; Vanderpump, 2004). One of the possible reason of this finding may be that this study has relatively small number of patients. Only female patients were included in this study could be another possible reason. It was observed that hyperthyroidisim rates in this study was also higher than literature (Smith & Hegedüs, 2016; Ursem et al., 2024). First of all, the fact that

Table 4. Laboratory values of non-diabetic, diabetic and prediabetic patients

Variables	Non-diabetic	Diabetic	Prediabetic	*p*
	(n= 4929; 83.7%)	(n=276; 4.7%)	(n=687; 11.6%)	
Fasting Glucose (mg/dl)	85±8	173±71	102±12	<0.001
HbA1c (%)	5.3±0.2	7.9±2.0	5.9±0.2	<0.001
TC (mg/dL)	183±44	210±46	200±47	0.021
LDL (mg/dL)	107±36	124±39	119±39	<0.001
HDL (mg/dL)	55±12	51±10	53±12	0.034
TG (mg/dL)	100±63	172±140	135±88	<0.001

TC: Total Cholesterol; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglyceride; fT3: free triiodothyronine; fT4: free thyroxine; TSH: Thyroid Stimulating Hormone

most of the studies in the literature were conducted in American and European countries may be one of the reasons for this difference. On the other hand, as mentioned in the study of De Leo et al. (2016) one of the possible reasons may be that the frequency of hyperthyroidism increases in regions with iodine deficiency.

This study has some limitations. First of them is that this study was conducted retrospectively. In addition, when searching the medical records of patients, only taking account of the disease codes entered in the hospital system creates another limitation.

Conclusion

It is our considered opinion that the rate of thyroid dysfunction and glucose metabolism disorders may be higher in our country compared to other countries in the world. We therefore believe that further studies on this subject should be carried out, with the aim of emphasising the importance of diet, exercise and lifestyle changes. However, we believe that it would be beneficial for a healthy and young future population to consider opening special outpatients clinics for female patients in this age group in second and third level health institutions. This would enable us to monitor the metabolic parameters of women of reproductive age more closely and to carry out closer periodic follow-ups by family physicians.

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Ethics Committee Approval

Inonu University, Health Sciences Non-interventional Clinical Research Ethics Committee (Date: 07/01/2024 No: 2024/6032.

Informed Consent

None.

Peer-Review

Externally peer-reviewed.

Author Contributions

A.M.Y.: Contributed to the Manuscript on Design, Methodology, Data Collection, Data Analysis, Methodology, Writing - Original Draft and Read and Approved the Final Version of the Manuscript.

F.D.Y.: Contributed to the Manuscript on Design, Methodology, Data Collection, Data Analysis, Methodology, Writing - Original Draft and Read and Approved the Final Version of the Manuscript.

References

Atmaca, H. (2013). Hipotiroidizm. *Journal of Experimental and Clinical Medicine, 29*(4S), 301-308. https://doi.org/10.5835/jecm.omu.29.s4.017

Çakır, N. (2004). Gebelik ve tiroid hastalıkları. *Turkiye Klinikleri Journal of Endocrinology, 2*(1), 65-72.

De Leo, S., Lee, S.-Y, & Braverman, L.-E. (2016). Hyperthyroidism. *Lancet, 388*(10047), 906- 918. https://doi.org/10.1016/S0140-6736(16)00278-6.

Demir, N. (2017). *Gebelikte tiroid hastalıklarının tanı ve yönetim kılavuzu*. Maternal Fetal Tıp ve Perinatoloji Derneği. Retrieved from https://www.tmftp.org/files/ulusal/gebelikte-tiroid-hastaliklarinin-tani-ve-yonetim-kilavuzu-28092017.pdf

Halk Sağlığı Genel Müdürlüğü. (2019). *Erişkin bazı metabolizma hastalıkları (tiroid, osteoporoz, gut) ve çölyak hastalığı kontrol programı*. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü.

Hosier, H., Lipkind, H.-S., Rasheed, H., DeWan, A.-T., & Rogne, T. (2023). Dyslipidemia and risk of preeclampsia: A multiancestry mendelian randomization study. *Hypertension, 80*(5), 1067-1076.

Kızılırmak, P., Öngen, Z., Kayıkçıoğlu, M., & Tokgözoğlu, L. (2020). Evaluation of statin use on LDL cholesterol levels in Turkey: A systematic review. *Archives of the Turkish Society of Cardiology, 48*(2), 137-148. https://doi.org/10.5543/tkda.2019.45156.

Kirkegaard, S., Uldall Torp, N.-M., Andersen, S., & Andersen, S.-L. (2024). Endometriosis, polycystic ovary syndrome, and the thyroid: a review. *Endocrine Connections, 13*(2), e230431. https://doi.org/10.1530/EC-23-0431.

Krassas, G.-E., Poppe, K., & Glinoer, D. (2010). Thyroid function and human reproductive health. *Endocrine Reviews, 31*(5), 702-55. https://doi.org/10.1210/er.2009-0041.

Morselli, E., Santos, R.-S., Criollo, A., Nelson, M.-D., Palmer, B.-F., & Clegg, D.-J. (2017). The effects of oestrogens and their receptors on cardiometabolic health. *Nature Reviews Endocrinology, 13*(6), 352-364. https://doi.org/10.1038/nrendo.2017.12.

Satman, I., Omer, B., Tutuncu, Y., Kalaca, S., Gedik, S., Dinccag, N., Karsidag, K., Genc, S., Telci, A., Canbaz, B., Turker, F., Yilmaz, T., Cakir, B., & Tuomilehto, J. TURDEP-II Study Group. (2013). Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. *European Journal of Epidemiology, 28*(2), 169-180. https://doi.org/10.1007/s10654-013-9771-5.

Smith, T.-J., & Hegedüs, L. (2016). Graves' disease. *New England Journal of Medicine, 375*(16), 1552-1565. https://doi.org/10.1056/NEJMra1510030.

Stener-Victorin, E., Teede, H., Norman, R.-J., Legro, R., Goodarzi, M.-O., Dokras, A., Laven, J., Hoeger, K., & Piltonen, T.-T. (2024). Polycystic ovary syndrome. *Nature Reviews Disease Primers, 10*(1), 27. https://doi.org/10.1038/s41572-024-00511-3.

Türkiye Endokrinoloji ve Metabolizma Derneği. (2023). *Tiroid hastalıkları tanı ve tedavi kılavuzu* (7. baskı). Türkiye Endokrinoloji ve Metabolizma Derneği.

Türkiye İstatistik Kurumu. (2024, Mayıs). *Doğum İstatistikleri, 2023.* T.C. İçişleri Bakanlığı, Nüfus ve Vatandaşlık İşleri, Türkiye İstatistik Kurumu. https://data.tuik.gov.tr/Bulten/Index?p=Dogum-Istatistikleri-2023-53708

Uğurlu, G., & Aslan, D. (2023). Bir halk sağlığı sorunu: İyot yetersizliği. *ESTUDAM Public Health Journal, 8*(3), 541-545.

Ursem, S.-R., Boelen, A., Bruinstroop, E., & Elders, P.-J.-M. Gussekloo J, Poortvliet R. K. E, Heijboer A. C., den Elzen W. P. J. (2024). A Systematic review of subclinical hyperthyroidism guidelines: a remarkable range of recommendations. *European Thyroid Journal, 24*. https://doi: 10.1530/ETJ-24-0036.

Vanderpump, M.-P. (2004). The epidemiology of thyroid diseases. In L.E. Braverman and R.D. Utiger (Eds.), *The thyroid: A fundamental and clinical text* (9th ed., pp. 398-406). Lippincott Williams and Wilkins, Philadelphia.

Xiang, D., Liu, Y., Zhou, S., Zhou, E., & Wang, Y. (2021). Protective effects of estrogen on cardiovascular disease mediated by oxidative stress. *Oxidative Medicine and Cellular Longevity, 28*, 5523516. https://doi.org/10.1155/2021/5523516.