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Effect of *Laurusnobilis* Extract and Atorvastatin on Liver and Kidney function of Hyperlipidemia Male Rats

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Abstract

Introduction: Hyperlipidemia associated with increase of atherosclerosis and heart, blood vessels diseases. the present study was discuss of potentials effect of bay leave extract (BLE) and atorvastatin drug at diet with high fat, feeding rat types. **Material and Methods:** The Rats were randomly classificationfor 4 groups each group have 10 rats. control feed standard diet, group two rats feed HFD, group three rats feed HFD + (BLE 250mg/kg) and group four rats feed HFD + Atorvastatin 20 mg/kg in the experiment, the treatment done by gavage and treated with 4 weeks daily. **Results and Conclusion**: The results show increased significantly at the end body weights also the weight gain at group two by treated (HFD) , while hepatic levels was inhibited for the cholesterol, and also triglycerides, also the low-density lipoprotein cholesterol; While the hepatic levels and serum of high-density lipoprotein cholesterol may be increased when the animal treated 250 mg/kg BLE and 20mg/kg atorvastatin , also the result showed increased significantly in serum AST ,ALT, ALP, urea and creatinine in group of animals treated HFD , and caused decreased significantly in the value of above parameters when the animals treated 250 mg/kg BLE and 20mg/kg atorvastatin ,it reach the control. In conclusion, bay leave exerts and atorvastatin have amelioration effect against hyperlipidemia in HFD-fed rats.

Keywords: *Hyperlipidemia, Laurusnobilis, Atorvastatin, Lipid profile*

Introduction

Hyperlipidemia is specially called hypercholesterolemia, that is risk factor to increase for heart and blood vessels disease, hyperlipidemia, common of cause the mortality worldwide, it is high risk factor to many disease like related cardiovascular and atherosclerosis, which is include the coronary heart disease, and disease of brain, also myocardial infarction (IM), kidney failure which is major health problem at the world[1]. Lipids contain cholesterol, cholesterol esters, triglycerides and phospholipids. levels of LDL which is increased due to related to appear of atherosclerosis[2]. The removing cholesterol from tissues and highly protected against cardiovascular disease these by high density lipoprotein, resulted the hyperlipidemia means to high levels of lipids which are include the triglycerides and cholesterol or both at blood, high triglycerides concentration in blood means hyper triglyceridemia, but the cholesterol concentration in blood means hypercholesterolemia[3]. Other condition called dyslipidemia which is means abnormal metabolism of lipoprotein metabolism, which is related to increase production of lipoprotein or deficiency, these abnormalities lead to increase of total cholesterol in serum, triglyceride and low density lipoprotein concentration but low level of high density lipoprotein concentration, hyperlipidemia treated is reduce the risk of heart disease, blood vessels diseases and brain diseases [4]. The main source of cholesterol will not be diet, but about 80 % of cholesterol is formed in the body. The diet intake

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affects totally on the amount of cholesterol somewhat [5], the cholesterol may synthesized endogenously with organs such as liver and others organs. Some disease such as Endocrine disease most common to cause of hyperlipidemia[6], also hyperlipidemia can occurred due to an inherited disease such as in some breeds of dogs [7]. *Laurusnobilis* (bay leaf) (BL), called as laurel leaf, it is a fixture in cooking at many cuisines specially at Mediterranean also in the Americas, the leaves also ground before cooking, by leaf as plant used in many industrial, this used in many appliedsuch as drugs and foods also in cosmetics, the oils and leaves with dried which are used in food industry for adaptation meat products and fishes. It contain of essential oils about 1.3 percent. The leaves not permit growth of models, By leaves are pungent and taste with bitter if leaf is dried the aroma is herbal, also By leaves used in making of jerk chicken at Caribbean islands, the leaves was soaked and placed on col side for grill [8]. The term of tannin is a class of astringent, which is precipitate proteins and other organic compounds such as alkaloids and proteins, the compounds of tannin are distributed for several species of plants, they important in protection from predation also in regulation of plant growth, contraction from tannins is what lead to dry and pucker feeling in mouth throw the consumption of un ripened fruit, the tannins have the molecular weight vary from 500 to over 3,000 and up to 20,000 Daltons[9]. The Tanine derivative from part of plants which are found in market, it is cream colored powder, astringent taste and aromatic[10].

Material and Methods

The sample about 40 rats (male), the age between 6-8 weeks and the weight between 180-200 g the rats were collected in animal house of science college of Thi- Qar, by environmental control rats were housed in animal house about 12- hour light and dark remain for one week and the rats acclimatization before experiments.

Groups of animals lab: It classified to four of groups (n=10 per group) which are including the control group called (normal) one given normal slandered diet, the group two given diet with high fat, the group three the rats which is given HFD and treated with BLE 250 mg/kg and group four the animals given HFD and treated with atorvastatin 20 mg/kg; also the animals were given *ad libitum* access to diet with high fat for 4 of weeks, but not the normal group, maybe taking the control diet with end the rats were anesthetized also sacrificed.

Preparation of Bay leaf extract

Preparation of Bay leaf in the first carefully wash and dry of all leaves and put the leaves in container about half of bay leaves and oil and closed put the container in a pan and fill to 2 cm above of top container in the end bring to boil simmer slowly at two hours .

Results

Table (1), show is no significantly difference ($P>0.05$) in the body weight (initial) of all groups. Final body weight was significantly increased ($P<0.05$) in hyperlipidemia group as to compared by control and others groups with treated. Weight gain was significantly also increased ($P<0.05$) in group of animal given high fat diet to compare by control and others groups.

Table1. Effect of bay leave extract and atorvastatin on hyperlipidemia male rats on B.W gains (Mean ± SD) n= 10.

The treatment	Initial B.W. (g)	Final B.W (g)	Weight gain (g)
Group(control)	259.04 ±8.41 A	282.83±12.18 B	23.79 ± 1.41 b
HFD 2% cholesterol	261.42 ± 1.60 A	318.11 ± 1.23 A	56.69 ± 1.13 A
BLE 250 mg/kg	255.13± 10.86 A	279.11±12.45 B	23.98 ± 0.89 b
Atorvastatin 20 mg/kg	257.12 ± 1.7 A	293.42 ± 2.11 B	36.30 ± 1.53 B
LSD	N.S	13.44	6.21

Level of blood lipid

Table 2 show the level of blood lipid was significantly change that include total of cholesterol also triglyceride and low density lipo protein and high density lipoprotein, opposite to control group .The results in table revealed that HDL-cholesterol was significantly decreased ($P<0.05$) while total cholesterol, triglyceride and low density lipoprotein were increased significantly ($P<0.05$) in group with hyperlipidemia to compared with control and other of treated groups. Changes in lipid profile are reversed and their values became insignificantly ($P<0.05$) near the value of control group when rats treated by bay leave extract 250 mg/kg and 6.0 mg/kg of atorvastatin.

Table (2) Effect of bay leave extract and atorvastatin on hyperlipidemia male rats on serum Lipid Profile, (Mean ± SD) n=10

The groups	TC mg/dL	TG mg/dL	HDL mg/dL	LDL mg/dL
Control group	86.91±5.44 b	71.19±4.21 B	29.11±1.05 a	21.18±2.33 B
HFD 2% cholesterol	188.11± 4.14 a	171.13± 4.61 a	19.61±1.15 c	41.01±2.11 A
BLE 250 mg/kg	91.23± 5.11 b	68.14±4.19 B	28.91±1.25 B	20.18±2.71 B
Atorvastatin 20 mg/kg	89.01±4.61 b	62.052±3.81 B	33.17±1.13 A	19.34±3.185 B
LSD	6.14	4.65	3.07	3.24

Liver function test:

As illustrated in table (3) the results of enzyme ALT and AST in serum were significantly increase ($p\leq0.05$) in HFD and group of animals treated 20 mg/kg bw atorvastatin compared with control and group of animal

treated extract of BLE with 250 mg per kg of body weight, also the table showed ameliorative effect of BLE 250 mg/kg.Bw and 20 mg/kg Bw. atorvastatin in ALP enzyme when appeared increased significantly in group of animals treated HFD to compared by control group .

Table (3): Effect of bay leave and atorvastatin about the ALT, AST and ALP enzyme Mean ± SD) n=10

Groups	ALT (U/L)	AST (U/L)	ALP (IU/L)
Control	25.51± 1.87 C	19.06±1.03 C	25.32± 2.48 B
HFD 2% cholesterol	52.17± 4.51 A	56.18± 4.45 A	36.28 ± 2.41 A
BLE 250 mg/kg	24.12± 1.21 C	20.06± 2.01 C	26.18 ± 1.07 b
Atorvastatin 20mg/kg	33.33±2.14 B	28.62±1.81 B	28.17 ± 2.41 B
LSD	3.23	4.25	3.65

Kidney function

A significantly p-value ($p \leq 0.05$) increased concentration of serum urea in blood concentration was noticed at treated the animals by HFD compared to control and rats treated by bay leave extract 250 mg/kg and 6.0 mg/kg of atorvastatin table (4). Also these tables show significantly p-value ($p \leq 0.05$) increased concentration of serum creatinine was recorded at HFD animal's treatment compared with control and other treated groups.

Table (4) : Effect of bay leave and atorvastatin on urea and createnin. (Mean ± sd) n=10

Group	Urea mg/dL	Creatinen mg/dL
Control	21.25± 2.18 C	0.51±0.02 B
HFD 2% cholesterol	61.57 ± 3.86 A	1.12 ± 0.13 A
BLE 250 mg/kg	28.72± 3.15 B	0.31± 0.01 C
Atorvastatin 20mg/kg	18.55±1.89 C	0.22±0.08 C
LSD	3.11	0.11

Discussion

Objective of the study was comparing *Laurusnobilis* extract with Atorvastatin on the rats as type of diet with high fat (HFD). Induced hyperlipidemia caused increased in weigh and weigh gain. The results agree with Cláudia and his coworkers [11], they obtained that diet with high fat lead to improve energy ingestion, also the weight gain, and body fat mass. Feeding Rats by diet with high fat taking with higher amounts of food, also the higher amounts for energy with study when discussed group the feeding rats with the standard of the diet. The body weight gain was higher at those animals and may be due to relaxation of the adipose tissues, also maybe high fat diet effect on the Leptin which is hormone adipocyte-derived which controls on food intake and expenditure of energy[12] .The concentration of leptin in plasma increased at proportion of body fat mass. Diet with high fat of feeding in rodent related to increase in consumption of food[13].Mechanism of overeating, (hyperplasia) and subsequent weight gain in diet with high fat fed animal types and human results a matter of debate[14]. In our study that the methanolic leaf extracts of *Laurusnobilis* administrated that ameliorate increased of the body weight gain in group with hyprlipidaemia. Due to that *Laurus with leaf* extracts increase the c lipids which is accumulated in adipose tissue resulting in ameliorate body weight. For our study, increased significantly body weight of rats treated with atorvastatin with statin use the weight gain not well explained, other results that showed used of the statins lead to large of body and accumulation of hepatic fat at rats with obesity[15]. Other study done by [16] was reported the weight of body increased post one year of atorvastatin randomization. Term of hypercholesterolemia associated with high concentration of low density lipoprotein and low concentration of high density lipoprotein concentration is common factor for development of atherosclerotic disease, more diet-derived cholesterol is the first cause of hypercholesterolemia[17]. At present study, the rats feeding with diet high fatto 4 weeks exhibited this lead to increase levels of TC and LDL concentration at serum More of data not coordinate with others similar studies[18] Most resulting of this study showed consumption of BLE daily at doses of 250 mg/kg and Atorvastatin 20mg/ kg that improve the serum of hepatic lipid profile, better hepatic function tests, and haptic enzymatic system at diet with high fat on feeding rat type. On the other hand, Atorvastatin known as of 3-hydroxy and 3- methylglutaryl coenzyme A that for reducates inhibitors with very effective on lipid-lowering effects in human and animals[19]. Our results also explain that the hypercholesterolemia may be leads to production of fats but not affecting liver function. Other groups of researchers which are using more of diet supplementation showed large severe form of liver injury, it means liver fibrosis that because isolated hypercholesterolemia induced by diet which containing 2 % of cholesterol, for 2 weeks in Westar rats[20]. Present findings to confirm these aforementioned studies showing that isolated of hypercholesterolemia lead to liver injury, presence of cholesterol in diet is necessary for triglyceride accumulation in the liver, as 5 % dietary fat alone has no such effect [21]. The BLE treated group showed decreased ALT, AST and ALP enzyme level that maybe due to hepato protective properties of the BLE. That is probably due to presence and combined action of the extract phytocomponents which have non flavonoid in origin such as, terpenes and terpenoids possessing anti oxidative also antimicrobial activities[22].

The statins mainly in the liver are metabolized and increase the levels of aminotransferases with liver potential toxicity that may be attributed to alteration of hepatocyte cellular membrane rather than direct liver injury, the increased level of ALP also AST and ALT that indicate these enzymes outside from liver into the blood stream and indicated the tissue was harm, which is associated

with necrosis of liver[23]. Alanin amino transferase is found throughout the cytoplasm, whereas part at amino transferase is found in the mitochondria. In case of liver stress, mitochondria damage with ROS accumulation tends to increase the level of AST rather than ALT [24].

Conclusion: bay leave exerts and atorvastatin have amelioration effect against hyperlipidemia in HFD-fed rats.

Conflict of Interest: Nil

Source of Funding: Self

Ethical Clearance: It was given by the institution.

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Anti-obesity and Hypolipidemic Effects of *Morus alba*- A Review

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Abstract

The prevalence of obesity was worldwide increase in the last 60 years. Obesity represented one of the public healthproblems, it markedly increased the incidence of many diseases:fatty liver,type 2 diabetes, hypertension, ischemic heart diseases, sleep apnea, osteoporosis, dementia, tumors and many other disorders.Recent reviews showed that many medicinal plants possesses anti-obesity effect.In the current review, PubMed, Web Science, Science Direct, Researchgate, Academia.edu and Scopus were searched to verify thehypolipidemic and anti-obesity activities of *Morusalba*.

Key words: *Anti-obesity, overweight, hypolipidemia, Morus alba, Review*

Introduction

The prevalence of obesity was worldwide increase in the last 60 years. Obesity represented one of the public health problems, it markedly increases the incidence of many diseases: fatty liver, type 2 diabetes, hypertension, ischemic heart diseases, sleep apnea, osteoporosis, dementia, tumors and many other disorders.Therefore, it deteriorated the quality of life. Behavioral interventions and lifestyle changes aimed toincrease energy expenditure andreduce the caloric intake showed limited efficacy because of complex etiology (hormonal, metabolic, and neurochemical). Many drugs were also used to suppress their appetite and avoid overeating[(1)].In the current review, PubMed, Web Science, Science Direct, Researchgate, Academia.edu and Scopus were searched to verify thehypolipidemic and anti-obesity activities of *Morusalba*.

Morusalba

Morus alba (Family: Moraceae) fruits were used traditionally as anthelmintic, antibacterial, sedative, analgesic, antirheumatic, diuretic, hypotensive, hypoglycemic, purgative, restorative, tonic, and hypolipidemia[(2-6)]. The phytochemical analysis showed that the plant contained tannins, steroids, phytosterols, sitosterols, glycosides, alkaloids, carbohydrates, proteins and aminoacids, flavanoids, phenolics, anthocyanins, anthroquinones, saponins, triterpenes, and glycosides[(7-10)]. The fruits contained protein 1.55g, lipids 0.48g, crude fiber 1.47g; and total carbohydrates 14.21g/100g dry weight. The Total sugar content was 7.55g, ascorbic acid 15.2mg, riboflavin 0.088mg, niacin 3.10mg/100 g fresh weight. The total phenolic contents was 7.7 to 11.2mg GAE/g, and total flavonols 0.07 to 0.51 mg/g dry weight [(11)]. The elements and minerals detected in the fruits were: N 1.62-2.13, P 0.24-0.31, K 1.62-2.13, Ca 0.19-0.37, Na 0.01, Mg 0.12-0.19, S 0.08-0.11g/100 g. While, the fruits contained Fe28.2-46.74, Cu 4.22-6.38, B 13.78-19.48, Mn 12.33-19.38, Zn 14.89-19.58 and Ni 1.40-2.62 mg/kg[(12)].

The freeze-dried powder of mulberry fruits contained phenols 23.0mg/g GAE, flavonoids 3.9

mg/g rutin equivalents and anthocyanins 0.87mg/g cyanidin-3-glucoside equivalents.Rutin (0.43mg/g), morin (0.16mg/g), quercetin (0.01mg/g) and myricetin (0.01mg/g) represented the main flavonol in the fruit powder [13].

However, anthocyanins content of the fruit ethanol extract was 137 to 2057 mg malvidin-3-glucoside equivalents/kg[14]. Anthocyanins isolated from the fruits included cyanidin 3- glucoside, cyanidin 3-*O*-*β*-D-glucopyranoside, cyanidin 3-rutinoside, cyanidin 3-*O*-(6-*O*-*α*-rhamnopyranosyl-*β*-D-glucopyranoside), cyanidin 3-*O*-(6- *O*-*α*-rhamnopyranosyl-*β*- D- galactopyranoside), cyanidin 3-*O*-*β*-D-galactopyranoside and cyanidin 7-*O*-*β*-D-glucopyranoside[15-16].

Flavonoids identified in the fruits were astragalin, nicotiflorin, quercetin, isoquercitrin, morkotin A and C, rutin, kaempferol 3-O- (6- O- malonyl) glucoside, kaempferol 3,7-di-O-glucoside, quercetin 3, 7-di- O- glucoside andquercetin 3-O-(6-O-malonyl) glucoside[17].The total phenolic contents of*Morus alba* leaves were 2.64 to 7.33 mg GAE/g dry weight and total flavonoids wer 0.95 to 2.39 mg QE/g dry weight. The polyphenols isolated from the fruits and leaves of *Morus alba*were: gallic acid, caffeic acid, chlorogenic acid, *m*-coumaric acid, *p*-coumaric acid, ferulic acid, vanillic acid, *p*-hydroxybenzoic acid, protocatechuic acid,syringic acid, protocatechuic aldehyde, syringealdehyde, kaempferol, epicatechin, and rutin[18-19].

The previous pharmacological researchesshowed that *Morus alba*exerted protective, neural, antiinflammatory, antimicrobial, analgesic, antipyretic, musculo-skeletal, immunological, antioxidant, antidiabetic, anticancer, cardiovascular, dermatological, gastrointestinal and respiratory the rapeutic effects.

Hypolipidemic and anti-obesity effects:

The antioxidant andhypolipidemicactivities of the root bark fractions of *Morus alba* were studied in rats fed high cholesterol diet. The results revealed that the administration of (50% methanol and 100% methanol) fractions ameliorated atherosclerotic state. Administration of 100% methanol fractionmarkedly restored the liver and plasma peroxides to normal limits, and significantly increased the resistance to at herogenic changes (44, 33, and 30% reduction in the LDL oxidation, LDL retention and LDL aggregation, respectively). Mulberroside A, albanols A and B and 5,7,2'-trihydroxyflavanone-4'-O-beta-D-glucoside were identified in the rootr and bark fractions[20].

Mulberry leaves extractcaused markeddecline in the triglycerides,LDL cholesterol and total cholesterol, and increased the serum level of HDL cholesterol in rats and mice[21-25].

The aqueous extract of Mulberry leaves at a dose of 150 mg/kg/day, for 14 days, significantly decreased the triglycerides level by 55.01% in rats on high cholesterol diet [26].

Morus alba leaves ethanol extractmarkedly decreased body weight gain, and diminished the elevated cholesterol, triglycerides, atherogenic index and coronary artery indices, it alsodecreased insulin resistance and glucose level in hyperlidemicrats induced by high- cholesterol diet (HCD). The serum leptin and resistinand their mRNA expression in visceral adipose tissue were significantly decreased by the extract, while, it increased serum adiponectin, and its expression significantly in visceral adipose tissue in hyperlipidemicrats[27].

MulberrosideA (MUL), the pure root ethanolic extract of Mulberry, and oxyresveratrol (OXY), prepared from MUL enzymatically, were studied (1-5mg/kg/day, for 4weeks) for their hypolipidemic effect in high cholesterol diet (HCD)-

induced hyperlipidemic, in triton WR-1339-induced hyperlipidemic rats, and normal rats. Triton-induced hyperlipidemic ratspretreated with MUL and OXY orally, showed decreased levels of serum lipidssignificantly. MUL and OXY in HCD-fed rats caused significant decline in lipids andatherogenic index. In addition, MUL and OXY induced significant amelioratedthe histological hepatic changesin HCDhyperlipidemic rats. Liver enzymes values were not significantly different in OXY-treated normal rats compared to water-treated rats[28].

The accumulation oflipid in the liver was decreased by *Morus alba* leaves extract, the number and the sizeof lipid droplets in hepatocytes were significantlyless than that in the control[22,24].

Flavonoids, phenolics and 1-deoxynojirimycin, isolated from the leaves of mulberry decreased plasma lipids by many mechanisms as detected by in vitvoand in vitro experiments. Kaempferol, quercetin, and 1-deoxynojirimycin enrichedleaves extracts activated the expressions of AMP-activated protein kinase and PPAR-a, and increased lipid breakdown and free fatty acid β-oxidation [23,29].

The leaves extract rich in polyphenol (quercetin, hydroxyflavin and caffeic acid)reducedlipogenesis by regulating of glycerol-3-phosphate acyltransferase, fatty acid synthase, liver X receptor and sterol regulatory element-binding proteins-1c [24, 30-31].

Moracin isolated from the leaves of *Morus alba* inhibited lipid peroxidation which strongly indicated its role as scavenger[26].

The antioxidants and hypolipidemic effects of the fruits of*Morus alba* were studied in hypercholestrolemic rats. The fruits of *Morus alba* at doses of 2.5, 5 and 10% caused significant increase in **the antioxidant activity** and significant decrease the total cholesterol, triglycerides, VLDL, and LDL cholesterol, with significant elevation in HDL cholesterol. [32].

The effects of mulberry leaves extract fermentedby *Cordycepsmilitaris* for 12 weeks, on the lipolytic activity, metabolism and accumulation of the lipids were measured in obesity induced in mice by high fat diet (HFD). The levels of total cholesterol, triglyceride, LDL cholesterol, and glucose were significantly decreased, and the level of HDL-cholesterol was significantly increased in high fat diet (HFD) + extract treated group compared with the HFD group treated with vehicle. The the size of adipocytes and the amount of abdominal fat were significantly decreased. The mRNA levels of (PPARγ)for adipogenesisin addition,Fas cell surface death receptor and adipocyte protein 2 were decreased after12 weeks treatmentwith the extract[33].

The effect of Ob-X, (contained: *Artemisia capillaries, Morus alba* and*Melissa officinalis*) on angiogenesis was determinedby miceMatrigel plug assay. Ob-X decreasedthe angiogenesis dose-dependently. Ob-X for 5 weeks in mice caused 27% reduction in bodyweight gain. Furthermore,The visceral adipose tissue and the size of adipocytes in visceral adipose were decreased by 46 and 15%, respectively. In addition, the treatmentalso significantly decreased the hepatic accumulation of lipids and the blood glucose levels [34].

The effect of leaves extract on oxidative stress induced by obesity, in addition to its effect on lipogenesis, hepatic fibrosis, was investigated in obese mice fed high-fat diet (HFD). The extract significantly decreased LXRα-mediated lipogenesis and hepatic fibrosis markers and up-regulated lipolysis-associated markers. Moreover, the extract restoredthe antioxidant enzymes activities in the HFD-fed mice[35].

The benefit of synergismbetween β-glucan and the leaf extract of mulberry on metabolic health were studied inmice fed high fat diet. β-glucanadministration

significantlydecreasedlipid profile, fat mass, fatty liver, body weight gain, insulin, and inflammatory markers. On the other hand, the administration of mulberry leaf extract possessed an efficacy similar to that of β-glucan (Ecept the effect on weight gain). Furthermore, a mixture of β-glucan and mulberry leaf extract showed synergism in improvement of insulin sensitivity [36].

The effect on food intake and weight of flavonoid standardized extract of *Morus alba* were evaluated in diet-induced obesity in the mice. The extract significantly and dose-dependently reduced the food intake in acute and prolongedtreatment. The extract (250mg/kg) decreased food intake by 58.6% and 44.8% and at a dose of 500mg/kg decreased food intake by 50.1% and 44.3% at 1 and 2 h after extract treatment. The high *Morus* root-bark extract dosecaused 16.5 and 22.5% loss in body weightat baseline and week 7, respectively, in obese mice with markeddecrease in visceral fat deposit and biochemical markers[37].

JS-MP-1, a polysaccharideidentified in *Morus alba* significantly decreased 3T3-L1 pre-adipocyte cells viability, reduced the ratio of the expression level of Bcl-2/Bax which induceddysfunction of mitochondria and preadipocyte cells apoptosis, and stimulated the cleavage of caspases 3 and 9 and poly polymerase. The apoptotic death appeared to be mediated by ERK and p38 signallingstimulation, which indicated that the polysaccharide was able to decrease the adipose tissue mass and the fat cells number via inhibition of proliferation of preadipocyte[38].

The anti-adipogenic and antioxidant effects of *Nelumbonucifera Morus alba* and *Raphanussativus* mixture were studied. The mixturedecreasedbody, adipose tissueand liver in high-fat diet. It decreased the glucose and lipid profile elevated by high fat diet. Blood glucose and seruminsulin growth factor-1, leptin and non-esterified fatty acid, were significantly declined, while, serum adiponectin was increased significantly[39].

When the 3T3-L1 cells treated by*Morus alba*ethanolic extracts at 100 microg/ml, the adipocyte differentiation was decreased by 18.6%. It decreasedC/EBPalpha expression and suppressed mRNA of PPARgamma in 3T3-L1 cells. A highest antiadipogeniceffect on 3T3-L1 cells was induced by ethyl acetate fraction. At a concentration of 100 microg/ml, the fraction decreased lipid accumulated intracellularlly by 38.5%. Protocatechulicacid which identified in the fraction, at a concentration of 100 microM, inhibited the accumulation of lipid by 44.8%, therefore the inhibition of lipid accumulation induced by the ethyl acetate fraction could be attributed to protocatechulic acid[40].

The pharmacological activity of UP601 (a mixture of *Morus alba, Yerba mate* and *Magnolia officinalis*extracts), was studied on changing of obesity-related parameters and biochemical markers in obesity induced in mice by high fructose (HFF). UP601 at a dose of 250 mcg/ml, induced a 1.8-times increase in lipolysis. UP601 decreased body weight by 9.1, 19.6 and 25.6% at doses of 300mg, 450mg and 600 mg/kg for 7 weeks in rats. The same doses caused reduction in the total cholesterol 9.1, 16.9 and 18.6%; in triglycerides 45.0, 55.0, 63.6%; in LDL 34.8, 37.1 and 41.6%; and in serum glucose 3.2, 21.6 and 33.7%, respectively. UP601 also caused 31.6% reduction in the body fat distribution and up to 89.1% decrease in the mesenteric fat [41].

UP601 (orally, 1.3 g/kg/day, for 7 weeks) was also studiedfor its appetite suppression and management of metabolic disorders in mice models. It caused markeddecreases in food intake 81.8, 75.3, 43.9, and 30.9% at 2, 4, 6, and 24 hours. Furthermore, it decreased body weight gain 21.5% VS 8.2%, at 7 weeks compared with untreated high fat diet-mice, decreased calorie intake 40.5% at the first week, reduced insulin and leptin by 75.9% and

46.8% , respectively, increased ghrelin level 4.2 times, and significantly decreased cholesterol and LDL. Mice treated by UP601 also showed less body fat, less mesenteric fat pad with an improvement of nonalcoholic steatohepatitis scores[42].

The acute, subacute and chronic toxicological studies in mice and rats showed that *Morus alba* was a safe remedy with high therapeutic index[7, 43-49].

Conclusion

*Morusalba*possessedmany therapeutic effects. The current review discuss its hypolipidemic and anti-obesity effect. *Morusalba*caused appetite suppression and exerted hypolipidemic and antiobesity effect by many mechanisms. Furthermore the toxicological studies revealed that *Morusalba*is an edible and very save remedy. It is a promising medical therapy with wide range of pharmacological effects.

Ethics approval and consent to participate

The work is a review, the authors didn't perform experimental and clinical work.

Consent for publication

The manuscript didn't contain any individual person's data.

Competing interests

The author confirm that this paper's content has no conflict of interests.

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Author's contributions

Both authors drafted the and approved the manuscript

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ORIGINAL ARTICLE

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Study of Intra Ocular Pressure Changes after Isometric Handgrip Exercise Test in Young Adults

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Abstract

Objective: ToStudy the effect of isometric handgrip exercise test on Intra ocular pressure in young adults

Method: Healthy young male adults in the age group of 18-22 years were selected among MBBS phase I students of a Medical college .Sample size was 40. Heart rate and IOP were recorded at rest and after isometric handgriptest

Results: Right eye IOP has decreased significantly from resting 16.28±1.55 to 9.30±1.79($p<0.001$) immediately after handgripexercise IOP Left eye IOP has decreased significantly from resting 16.15±1.69 to 13.04±1.19 ($p<0.001$)immediately after handgrip exercise IOP

Conclusion: Isometric handgripexercise lowers IOP which were significant. Hence may prove useful in normotensive glaucomatous patients

Key words: *Intraocular pressure, Handgripdynamometer*

Introduction

The Intra Ocular Pressure [1] (IOP) is important in maintaining shape of the eye ball and optical integrity. IOP is known to be sensitive to many physiological variables in the body system which include age ,sex, body position, valsalvamanoeuvre ,exercise, diurnal variations and pregnancy.

Exercise when performed regularly has beneficial effect on various systems of individual like physical, metabolic, and psychological. These physiological variables in body system include changes in vascular pressure, serum osmolarity, hormonal levels, decrease in blood pH ,increase in blood lactate and presence of toxins.

It is well documented that improvement of physical fitness through regular exercise can produce physiological change in the whole body especially in the cardiovascular system.

In recent years it has been documented that IOP is a dynamic function and is subjected to many influences both acutely and over long term.IOP is also known to be responsive to short- term and long- term exercise.

Glaucoma is chronic progressive optic neuropathy caused by a group of ocular conditions which lead to damage to optic nerve with loss of visual function. Most common risk factor is raised intraocular pressure[1,4,5] Relationship between isokinetic exercise &IOP showed significant lowering of IOP after exercise[2,3]

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Aims & Objective

ToStudy the effect of isometric handgrip exercise test on Intra ocular pressure in young adults

Materials and Methods

Healthy young male adults in the age group of 18-22 years with BMI of 18-22.9kg/m^2 were selected among MBBS phase I students of a Medical college .Sample size was 40. Heart rate and IOP were recorded at rest and after isometric handgriptest.

The subjects were requested to complete a questionnaire that included inclusion and exclusion criterias. Then physical examination was carried on each participant to rule out any systemic diseases affecting IOP. The weight, height, were measured and BMI was calculated by using formula weight in kgs / the square of height in meter. Subjects fitting the inclusion and exclusion criterias (n =40) were considered for the study. Overweight subjects (BMI-23-24.9 kg/ m2) and subjects with refractive errors were excluded.

Inclusion Criteria

v Young healthy adults in the age group of 18-21yrs of both sexes.

v Non obese BMI 18 – 22.9 kg/ m2.

v Normotensive < 130/80mm Hg.

v Non smoker

v Non alcoholic

Subjects with Pre-existing refractive error, acute and chronic Conjunctivitis, Glaucoma, Migraine were excluded from study[7]

Materials:

· Power lab ECG.

· Schiotz tonometer

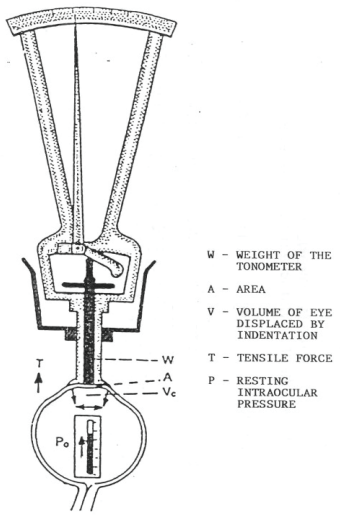
· Handgripdynamometer

AD Instrument Powerlab (Model-ML870, Serial-830-0732):

AD Instruments provides computer-based data acquisition systems for research andeducation. Powerlab data acquisition systems and choice of LabChart, LabTutor and LabAuthor software, provide outstanding data acquisition, display, analysis and authoring features for a wide range of life science applications. Since 1988, Powerlab (also MacLab) systems have been used for data acquisition and analysis by the world's best academic, government and private organizations.Powerlab systems combine software-controlled input of parameters, extensive signal conditioning options, variable sampling speeds and powerful real-time computations with the advantages of computer-based data display and analysis. They offer the functionality of a chart recorder, XYT plotter, digital voltmeter and storage oscilloscope in one compact unit. LabChart software, supplied with Powerlab systems helps in analysing the data. In the present study by using Powerlab Heart rate measurement was done on subjects in supine posture.

Basic concept and theory of indentation:

Schiotz tonometry is based on the fundamental fact that a plunger will indent a soft eye more than a hard eye. When the tonometer is placed on the cornea, immediately the different forces come into play; W-the Weight of the tonometer, acts over an area A and indents the cornea displacing a volume V. The tensile force T set up in the outer coats of the eye at every where tangentially to the corneal surface, with a component opposing W, so that an additional force T is added to the original baseline or resting IOP (P0) which is artificially raised to a new value (. Thus the scale reading of the tonometer actually measures the artificially raised IOP



Hand grip dynamometer :

The device used to measure the grip strength is called dynamometer. It is reliable and valid in evaluation of grip strength. It is widely accepted and grip strength measurements provide an objective index of the functional integrity of the upper extremity. Measurement of grip strength by hand dynamometry is reproducible and consistent. The handgrip dynamometer is easy to handle and reliable in its measurements.

Parameters

Study was carried out in physiology department

· Intraocular pressure in mm hg in supine position using standard steps.

· Weight in kilogram. & Height in meters were measured. BMI=Weight in kg/height in meter^2 was calculated to group them as normal weight.

· Heart rate

· Maximum voluntary contractions(MVC) was assessed and subjects were asked to carry out endurance isometric exercise at 40% of their MVC

Study method –.

Prospective study.

Ethical clearance was obtained from our institution Ethical committee

Prior to the procedure written and informed consent was obtained from all the subjects..

The exercise was performed in a well-ventilated room. Participants were instructed not to consume beverages nor a heavy meal in previous 4hours or participate in any vigorous activities 24 hour before test

Isometric endurance contraction at 40% of the individuals MVC was executed with handgripdynamometer

In order to minimize the bias of diurnal variations of IOP and other parameters, the studies were made between 3pm to 4pm.

At the reporting time subjects were asked to relax in supine position for 5min. Baseline IOP was recorded .Subjects executed MVC contractions of 1second duration at 1 minute interval for 3times .Maximum of these is considered as their MVC .Then endurance contraction at 40% of their MVC is made. Intraocular pressure and Heart rate were measured in supine position immediately (within 30 sec), at five, at ten, at fifteen minutes after exercise.

Statistical Analysis

Mean and Standard deviation was calculated for isometric hand grip exercise test in young adults. Paired t-test was applied at 5% level to test the significance of changes in above parameters(Using Epi-Info) Microsoft Excel and EPI-INFO package

were used for data entry and statistical analyses respectively.

Results

Mean and SD of IOPof right &left eye after Isometric handgrip Exercise

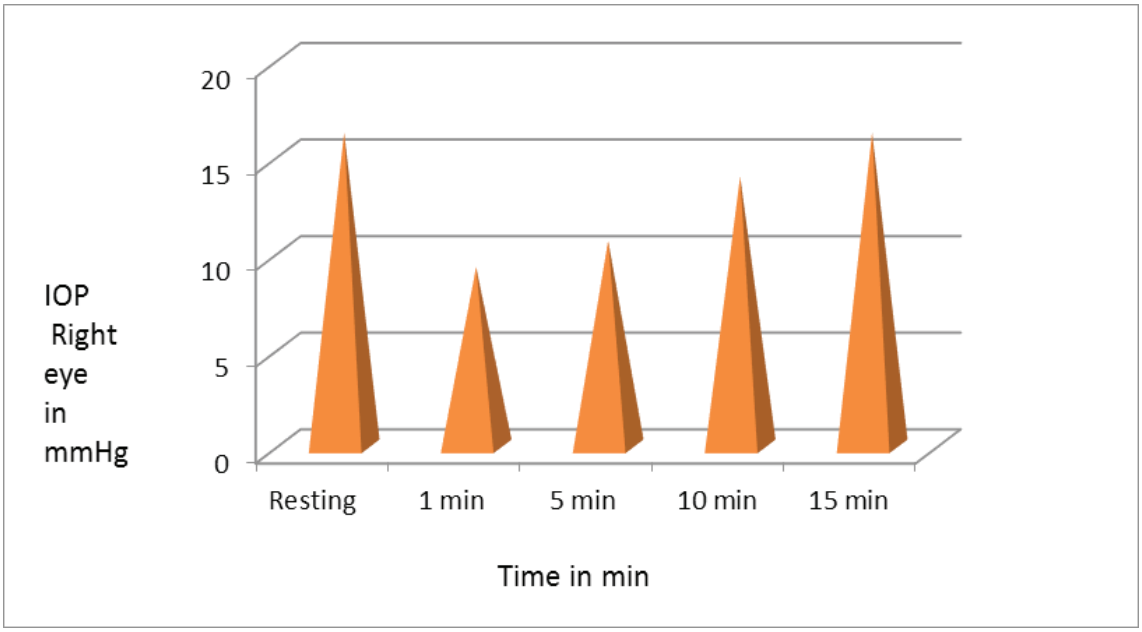
Parameter	Duration	Hand Grip	P value
Right eye IOP	Resting 1 min exercise 5 min postexercise 10 mipostexercise 15 min pt exercise	16.28±1.55 9.30±1.79 10.67± 1.90 13.99±1.32 16.26±1.57	>0.05 <0.001* <0.001* <0.001* >0.05
Left eye IOP	Resting 1 min exercise 5 min postexercise 10 mipostexercise 15 min pt exercise	16.15±1.70 8.91±1.74 10.60±1.92 13.74± 1.71 16.15±1.69	>0.05 <0.001* <0.001* <0.001* >0.05

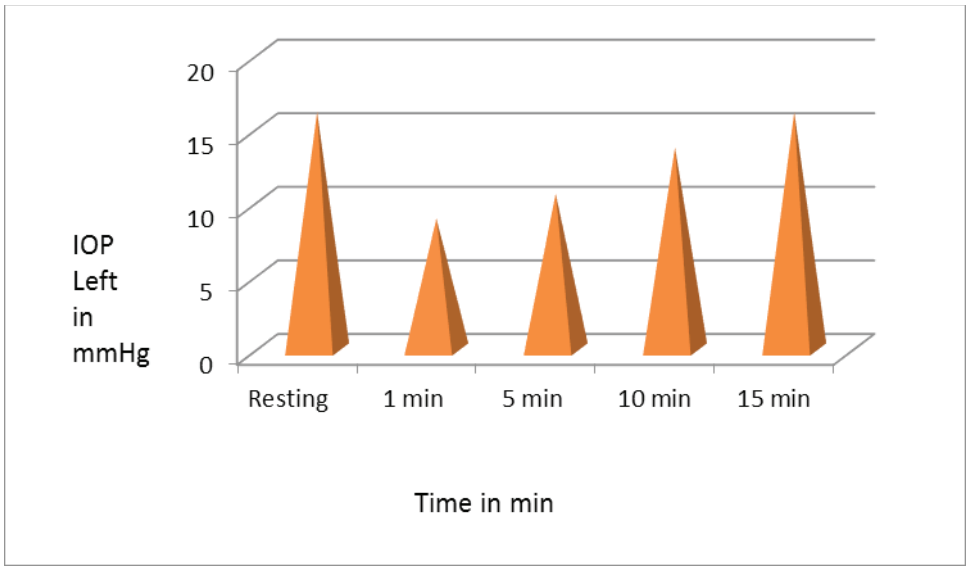
Data presented as mean& SD

*Statistically significant $p < 0.05$

Right eye IOP has decreased significantly from resting 16.28±1.55 to 9.30±1.79($p<0.001$) immediately after handgripexercise IOP has returned back to resting level within 15 min after exercise.

Left eye IOP has decreased significantly from resting 16.15±1.69 to 13.04±1.19 ($p<0.001$) immediately after handgrip exercise IOP has returned back to resting level within 15 min after exercise.





Discussion

- Isometric handgripexercise stimulate ocular sympathetic nervous system to increase the facility of outflow and thus decreases IOP . Also epinephrine stimulates synthesis of cAMP. Activation of cAMP decreases IOP by decreasing aqueous humour production[6,8]

- Also Afterhandgripexercise there is rise in blood lactate levels. Increased Lactate levels causes outflux of water from eye which is responsible for fall in IOP [9]

- Low CO_2 tension in blood is associated with a reduction of IOP after isometric (anaerobic) exercise. In his study Harris compared the drop in IOP in 2 sets of individuals. In first set subjects were made isocapnic during exercise by giving carbon dioxide and in second set subjects were not given carbon dioxide and thus stayed hypocapnic. They observed cessation in IOP drop with blockage of exercise induced hypocapnia in first set and claimed the presence of this indirect effect of exercise of reduction in IOP by inducing hypocapnia[10]

Conclusion

Isometric handgripexercise induces raise in heart rate and simultaneously lowers IOP and both were significant. Hence may prove useful in normotensive glaucomatous patients.

Conflict of Interest : None

Source of Funding : Self

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Study of Cardiovascular Parameters and Heart Rate Variability (Frequency Domain Analysis) In 1St Trimester of Normal Pregnant Women and Pregnant Women with Risk Factors for Pih in Western Rajasthan

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Abstract

Background: The role of sympathovagal imbalance (SVI) and CV risk in pregnancy-induced hypertension (PIH) has been reported, and their association during early trimesters of gestation in PIH has not been studied. Therefore, in the present study, we have investigated the maternal cardiovascular parameters and frequency domain indices of Heart rate variability (HRV) between normal pregnant women and women with risk factors for PIH in their 1st trimester of gestation.

Methods: Two hundred twenty subjects each (220 of normotensive pregnant women i.e., control group and 220 of pregnant women with risk factor for PIH i.e., study group) of 1st trimester of gestation were recruited from the obstetrics & gynecology department of Umaid hospital, associated with Dr. S. N. Medical College, Jodhpur, Rajasthan. Physical examination was done and anthropometric measurement like height & weight were taken. The collected data was statistically analyzed using HRV analysis software.

Results: Significant difference in body mass index was observed between the two groups. Systolic blood pressure, Diastolic blood pressure, Pulse pressure, Rate pressure product and Mean arterial pressure of study group was significantly higher than control group. Values of LF and LF/HF ratio components of frequency domain analysis of HRV were significantly increased but HF component is non significantly decrease in 1st trimester of the pregnant women with risk factor for PIH than normal pregnant women.

Conclusion: The present study indicates that the cardiovascular parameters in 1st trimester of pregnant women with risk factor for PIH were increased highly significantly than the normal pregnant women. The highly significant (HS) ($p<0.000$) increase in the LF (nu) & LF/HF ratio and non significant (NS) ($p<0.552$) decrease in HF (nu) of pregnant women with risk factors for PIH was observed than normal pregnant women this indicate that sympathetic tone was increased in 1st trimester of pregnant women with risk factor for PIH. Vagal withdrawal and sympathetic exaggeration may be the possible cause of PIH in pregnant women with its risk factors.

Keywords: *PIH, Heart Rate Variability, pregnancy, autonomic nervous system*

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Introduction

Severe HTN during pregnancy raises the risk of heart attacks, cardiac failure, cerebrovascular accidents, and renal failure in the mothers [(1)]. In India, the incidence of PIH is reported to be 8-10% among

pregnant women. According to a study, the prevalence of PIH was 7.8% with preeclampsia is 5.4% of the study population in India.

The exact pathophysiology of PIH is not known but low circulating volume and high vascular resistance is well established charecteristics of this disease [2,3]

Impairment of the autonomic nervous system functions may be the cause of PIH. [4] Although there is still a debate regarding whether PIH is associated with disturbances in the sympathetic and parasympathetic functions of the autonomic nervous system [5] Heart Rate Variability (HRV) analysis test can be used to evaluate changes in ANS during different pathophysiological conditions.

In recent year heart rate variability (HRV) is powerful tool for quantitative assessment of cardiac autonomic function, as an indicator of autonomic nervous activity and index of cardiac autonomic regulation.[6-8] It is well established that high-frequency (HF) of HRV is mediated by parasympathetic nervous system (PNS) modulation [9-11] whereas low-frequency (LF) reflects both sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) autonomic influences.[12,13] The ratio of low-frequency power to high-frequency power (LF/HF) has been used to reflect cardiac sympathetic modulation (SNS indicator)[13,14]

Decreased HRV is a marker of cardiovascular autonomic dysfunction and a predictor for cardiovascular risk and increased mortality [15, 16]; it can be used as a sensitive tool in the early detection of PIH in pregnant women with risk factors for PIH. But very few studies have been done on it, thus the main objective of our present project was to compare the maternal HRV (frequency domain parameters) changes between normal pregnancy and pregnancy with risk factors for PIH.

Material & method:

The present study was conducted in the Upgraded department of Physiology in Dr. S. N. medical college and hospitals, Jodhpur. Subjects (control group and study group) were recruited from the out-patient unit of the Obstetrics and Gynecology Department of UMAID hospital associated with Dr. S. N. Medical College. Before starting study all ethical consideration for the subjects were taken in accounts and written permission was obtained from institutional ethical committee. A written consent was obtained from each subject. Sample of the 440 women (220 normal pregnant women and 220 pregnant women with risk factor for PIH) were collected during the October 2019 to December 2019.

Subjects of study group included pregnant women who had risk factors for PIH so inclusion criteria for the study group included established risk factors for PIH such as

1. family history of preeclampsia,
2. preeclampsia in previous pregnancy,
3. extremes of reproductive age, and
4. BMI ≥30.

Subjects of control group included pregnant women who had none of above mentioned risk factors for PIH. All the subjects were examined and detailed personal history was taken with reference to smoking, alcohol intake, family history of hypertension, socioeconomic status, place of residence etc. All subjects had to fill a proforma. Physical examination was done and anthropometric measurements like height and weight were taken and BMI was calculated.

The subject was advised to take complete bed rest in supine position for 10 minutes in a cool and calm environment and not to take and perform any physical or mental activity. Blood pressure was recorded using

mercury sphygmomanometer. The recording of short term HRV was done according to recommendation of the task force. After 10 minutes of supine rest in Polygraph laboratory of physiology department which was established in OPD of Obs. & Gyne. Department of UMAID hospital, all leads of HRV was placed over the subject in requisite position. Lead II of ECG was recorded for 5 minutes during supine rest using Physio Pac Digital Polygraph- Physiograph PL-2008, Medicaid 6 channel Systems, Chandigarh.

The data was transferred from Medicaid machine to window based computer with HRV analysis software. Frequency domain indices such as low frequency (LF), high frequency (HF) and LF/HF ratio (ratio of low frequency and high frequency) of HRV were calculated. In the frequency domain, LF power indicates a mixture of action of sympathetic and parasympathetic components on heart rate with a predominance of sympathetic ones, whereas HF power reflects parasympathetic modulation of heart rate [17, 18].

Statistical Analysis of Data

SPSS version 13 (SPSS Software Inc., Chicago, IL, USA) was used for statistical analysis. All data were expressed as mean ± SD. We used Student's unpaired t-test for the level of significance between the two groups.

Result

Table 1: The comparison of the cardiovascular parameters between normal pregnant women and pregnant women with risk factors for PIH.

Cardio vascular parameters (mm Hg)	1st trimester of Normal pregnant women (control group)	1st trimester of Pregnant women with risk factor for PIH (study group)	Normal v/s PIH risk factors women
	Mean±S.D	Mean±S.D	P value
SBP	104.99±5.89	120±9.913	<0.000↑
DBP	65.30±3.12	78.49±7.67	<0.000↑
MAP	78.53±3.50	92.32±7.78	<0.000↑
RPP	82.28±5.55	101.23±13.8	<0.000↑
PP	39.68±5.10	41.52±7.15	<0.000↑

The data presented are Mean±S.D. P value<0.01 was considered statistically highly significant

Table 1 is showing the comparison of SBP (mm of Hg), DBP (mm of Hg), MAP (mm of Hg), PP (mm of Hg) & RPP between the normal pregnant women and pregnant women with risk factors for PIH in their 1st trimester. The result shows the highly significant (HS) ($p<0.000$) increase in the SBP (mm of Hg), & DBP (mm of Hg), MAP (mm of Hg), PP (mm of Hg) & RPP of pregnant women with risk factors for PIH.

Table 2: Comparison of Frequency domain parameters between normal pregnant women and pregnant women with risk factors for PIH.

Frequency domain analysis	1st trimester of Normal pregnant women (control group)	1st trimester of Pregnant women with risk factor for PIH (study group)	Normal v/s PIH risk factors women
	Mean±S.D	Mean±S.D	P value
LF (nu)	30.55±4.91	39.27±5.8	<0.000↑
HF (nu)	33.37±9.88	32.84±8.8	<0.552↓
LF/HF	0.99±0.31	1.29±0.43	<0.000↑

The data presented are Mean±S.D. P value<0.01 was considered statistically highly significant.

Table 2 is showing the comparison of LF (nu), HF (nu) & LF/HF ratio between the normal pregnant women and pregnant women with risk factors for PIH in their 1st trimester. The result shows the highly significant (HS) ($p<0.000$) increase in the LF (nu) & LF/HF ratio and non significant (NS) ($p<0.552$) decrease in HF (nu) of pregnant women with risk factors for PIH.

Discussion

In the present study, the blood pressure measurement in the present study, had a highly significant increase in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Rate Pressure Product (RPP) and Pulse Pressure (PP) in the study group compared to the control group, which suggest that subjects having risks of developing PIH have altered CV parameters even in the early part of pregnancy, this may be due to their increased sympathetic discharge as PIH is first and foremost a state of sympathetic overactivity. So the cause of elevated blood pressure in PIH risk factor women in our study is may be sympathetic activation. This observation was supported by the study of Chaswal M. et al. (2018) [19], Subha et al (2014) [20] & G. K. Pal et al. (2011) [21].

The variables analyzed among the "Frequency Domain Measures" included in our study are "LF, HF, and LF/HF Ratio". As expected "Frequency Domain" variable LF which reflect both sympathetic and parasympathetic influence show highly significant ($p<0.01$) increase in 1st trimester of gestation of study group compared to control group, where as HF which mainly reflect parasympathetic influences was non significantly ($p>0.05$) lower in 1st trimester of gestation of study group compared to control group. "LF/HF Ratio" marker of sympathovagal imbalance (mainly depicts sympathetic dominance) was significantly high ($P<0.01$) in 1st trimester of gestation of study group compared to control group.

The current investigation likewise shows that in study group, patients have higher LF/HF ratio segments of "Frequency Domain Indices" which for the most part measures the sympathovagal balance to heart reflecting an increase in sympathovagal nerve action in PIH patients in starting of their pregnancy. The LF/HF ratio has been proposed to be a precise proportion of the general sympathovagal balance of the autonomic nervous system in which higher values demonstrate an all the more sympathetically driven cardiovascular system. Same results were obtained by the study of Chaswal M. et al. (2018) [19], A. Hossen et al. (2013) [22] G. K. Pal et al. (2011) [21]. The changes occurs in preeclampsia is not fully understood but few studies observed that some biologically active factors like cytokines or reactive oxygen species from placenta which inhibit vascular relaxation pathway or facilitates vascular smooth muscle contraction, may be responsible for hypertension in pregnancy.

Reports from various studies indicate that these placental factors cytokines and reactive oxygen species [23-25] released peripherally cross the blood-brain barrier and influence activities of various brain centers and their estimation may be helpful for further research. Although no intervention has yet proven effective for the prevention of PIH, early identification of women at risk for PIH may improve maternal and perinatal outcome. Screening for PIH is believed to be most relevant during the first trimester because preventive interventions (such as anti-platelet agents, calcium and antioxidants) are more likely to be effective if initiated early in pregnancy when pathogenic mechanisms may be modified. Further confirmation of the risk of future PIH based on HRV may enable closer prenatal monitoring, earlier diagnosis and prompt and appropriate management.

Conclusion

The present study conducted with the objective to compare maternal cardiovascular and HRV changes (frequency domain analysis) between normal pregnant women & pregnant women with risk factor for PIH it clearly indicates that the sympathetic activation may be the cause of elevated blood pressure in preeclamptic pregnant women of Jodhpur district. This study adds further evidence for the dominant cardiac sympathetic modulations in patients with risk factors for PIH compared with normal pregnant women, probably due to parasympathetic withdrawal in the study group. The frequency domain analysis of heart rate variability proved as a good tool in the study of preeclampsia. Significant increase in the LF and LF/HF ratio component of frequency domain indices was observed in pregnant women with risk factor for PIH than normal pregnant women this indicates that sympathetic tone was increased in study group. Our study on frequency domain analysis suggested that vagal withdrawal and sympathetic exaggeration may be the possible cause of PIH in pregnant women. Our study could have been better if this study would be conducted in different trimester of pregnancy. Further this study could be better if we estimate the levels of placental factors cytokines and reactive oxygen species in both the groups along with the level of proteinuria.

Ethical Clearance: Research involves human participants so ethical approval is obtained from Institutional ethics committee of Dr. Sampurnanand Medical College and Hospital, Jodhpur-. (IEC No.-18/15753).

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Conflict of Interest: nil

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Impact of Diabetes Type 2 in Adults on Autonomic Modulation at Rest and in Response to the Active Orthostatic Test

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Abstract

Background: Cardiovascular autonomic neuropathy Is one of the most common complications of Diabetes Mellitus Type 2(DM2). Heart rate variability (HRV} Is a noninvasive measure of cardiac autonomicmodulation. Reduced HRVIs an Independent cardiovascula rrisk factor and has been proposed as amarker of increased risk of mortality.Very few studies have measured Changesin HRV in DM2 in India.

Objectives: To analyze the autonomic modulation responses In DM2 patients by means of HRV indices.

Methodology: Across-sectional study of 20 Type 2 Diabetic mellitus from age groups 30-S0 years and age and gender matchenon-diabetic subjects as controls. Subjects satisfying in clusion and exclusion criteria and gave written informed consent were randomly invited to take partin the study. Initial assessment was done for HTN, hyperlipidemia, smoking, cardiovascular disease, family

H/o DM2, FBS >130 mg/di, Body mass index (BMI) >25 kg/m,DM2, duration of disease, and Heart rate.

Bloodpressure: measure dmercury sphygmomanometer aftera5-minrest. Electrocardiogram wasrecordedusingPower Lab• (ADlnstruments). The time domain, frequencydomainvariables, and nonli near parameters was meas ured from ECGusing Lab Chart• software.

Results and Conclusion : Time domain Variablesnamely AverageRR, SDRR,SDARR,rMSSD andPNNS0(%) and Frequency domain Variables; High frequency (HF) power, Low frequency (LF) power and Very Lowfrequency (LF)power Non-Linear Variables; S01and SD2 were reuced in patients with diabetes Mellitus compared to normal control but was not statistically significant. One of the reasons couldbesmallsamplesize. Study should be repeated in large sample size.

Key Words : *Heart Rate Variability, Autonomic Dysfunction, Type 2 Diabetic Mellitus*

Introduction

Diabetes mellitus is one of the most common Non-Communicable Diseases and, as well as the aging process, may influence the autonomic nervous system (ANS), leading to a poor autonomic control of heart [1,2]. In subjects with diabetes mellitus, damage to both parasympathetic and sympathetic fibers innervating the cardiovascular system produces the cardiovascular autonomic neuropathy (CAN). CAN clearly entails an increase in mortality and an acceleration of other

micro vascular complications [3]. Among the most common complications, it is highlighted the diabetic autonomic neuropathy which is poorly recognized and understood despite its significant effects on several organs and systems [4,5]. Heart-rate variability is a measure of cardiac autonomic function [6]. The heart rate variability (HRV) was proved to be a noninvasive tool as valuable clinical evidence for the prognosis of cardiovascular events and several disorders. Reduced HRV is an independent cardiovascular risk factor [7, 8]. At an early-stage autonomic dysfunction may be asymptomatic or mildly symptomatic. Symptomatic autonomic neuropathy carries worst prognosis, so early diagnosis is essential for maximum benefit more so in Diabetes [9]. Also, very few studies have measured changes in Heart Rate Variability in type 2 diabetes mellitus in India. Thus, analysis of HRV associated with the autonomic active orthostatic test is important in South Indian population. Hence in the present study our aim is to analyze the autonomic modulation responses induced by the implementation of the active orthostatic test, in adults with DM2, and study the autonomic modulation by means of HRV indices.

Objectives

1. To determine HRV in type 2 Diabetics Mellitus.

2. To determine Autonomic modulation responses induced by the implementation of active orthostatic tests in adults with type2 diabetics mellitus.

Material and Methods

A cross sectional study of 20 type 2 Diabetes Mellitus patients from age groups 30-50 years and 20 age and gender matched non-diabetic subjects as controls.

Inclusion criteria

Patients with Diabetes Mellitus type 2 minimum disease duration>2 year with controlled glycemic status defined as (1) glycosylated hemoglobin (HbA1c)<7 mg % (2) FBS<126 mg% and (3) post prandial blood sugar <180 mg % (ADA guidelines)

· On regular hypoglycemic medication but not insulin

· Patients who are ready to give written informed consent

Exclusion criteria

· Those on irregular treatment, newlydiagnosed (<6 months)

· Previous h/o neurological or cardiovascular intervention, onpacemaker, on drugs directly affect ANS, arrhythmia

Initial assessment was done for Hypertension, Hyperlipidemia, Smoking, Cardiovasculardisease, family h/o diabetes mellitus, FBS>130mg/dl, BMI>25kg/m2, duration of diabetes mellitus and Heart rate.

Assessment of HRV was carried out between 8.30 and 12.00 am in a separate examination room. Patients were requested to avoid coffee, tea, cola drinks, and smoking for 12 h and alcoholic beverages for 24 h before the procedure

Blood pressure was measured by mercury sphygmomanometer after a 5 min rest.

Electrocardiogram was recorded after supine rest for at least 5 min with subject being in supine position and breathing freely using power lab (AD Instruments). The ECG recording from the precordial leads was transferred online to a microcomputer for the analysis of HRV.

Heart rate variability was measured from ECG using Ad instrumentslab chart software

Autonomic Test—Active Orthostatic Test

To perform the active orthostatic test the subjects will be instructed to remain lying at rest for 30 minutes, after which they will stand up (3 to 4s), remaining in a standing position for 10 minutes. The subjects will be monitored throughout the period. The RR interval sequence with greater stability was selected from the initial rest period and during the maneuver for each subject

Statistical Analysis

The statistical significance of differences in the mean distribution of various parameters among various subgroups is done by Mann–Whitney test or unpaired Student's *t*-test for quantitative data.

Time Domain Variables

- Average RR: Mean RR Interval
- SDRR: Standard deviation of R-R Interval
- SDARR: Standard deviation of average R-R Interval
- rMSSD: Root mean square of successive RR interval differences
- PNN50(%) time domain heart rate variability

Frequency Domain Variables

- High frequency (HF) power
- Low frequency (LF) power
- Very Low frequency (LF) power

Non-Linear Variables

- SD1
- SD2

Results

FIGURE 1

DIAGRAM 1 SHOWING GENDER DISTRIBUTION OF SUBJECTS

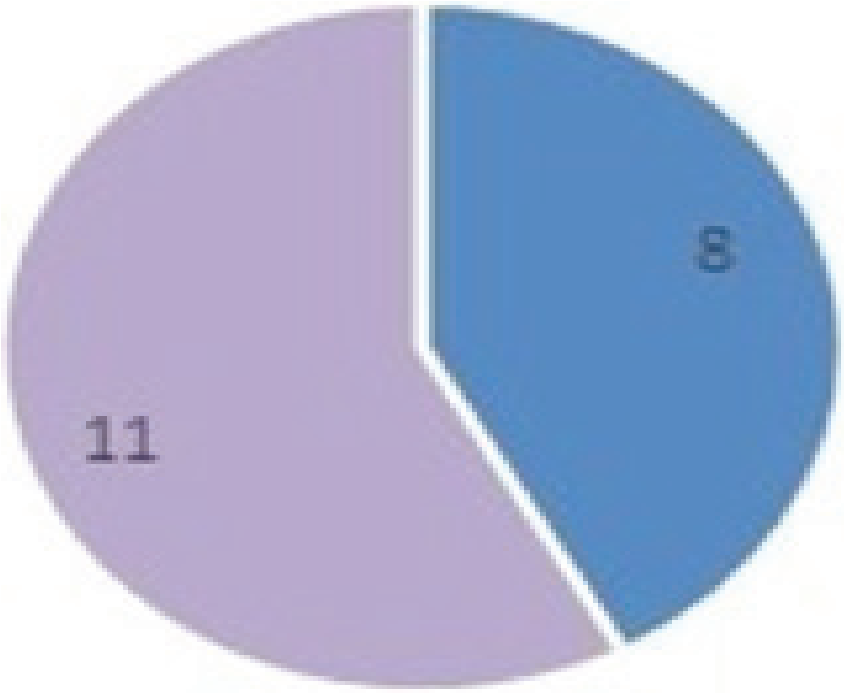

DIAGRAM 2 SHOWING DISTRIBUTION OF SUBJECTS INTO DIABETICS AND NON-DIABETICS

Table-1: Comparison of Time, Frequency Domain and nonlinear variables in diabetic and non-diabetic patient

	Parameters	Diabetic		Non diabetic		P value
		Mean	SD	Mean	SD	
TIME DOMAIN	Average meanRR (ms)	826.41	129.18	774.96	86.15	0.311
	SDRR (ms)	51.87	10.78	71.71	66.06	0.772
	rMSSD(ms)	48.56	18.73	73.68	118.61	0.386
	PNN50(ms)	14.66	11.93	21.17	22.95	0.96
Frequency Domain	HF power(ms2)	39.96	20.40	29.79	19.43	0.26
	LF power(ms2)	26.83	11.70	31.07	13.82	0.49
	VLF power(ms2)	29.71	18.61	36.54	20.04	0.46
Nonlinear Domain	SD1(ms)	35.52	11.82	52.29	83.91	0.30
	SD2(ms)	64.73	14.91	79.30	52.98	0.96

Discussion

Heart rate variability (HRV) asserts the variations of instantaneous HR as well as RR intervals. Decreased HRV is a recognized vital autonomous risk element for greater mortality and sudden cardiac death (SCD) in cardiovascular disease and healthy populations [10]. In about half of the patients, diabetesmanifests as autonomic neuropathy leading to autonomic imbalance which is a bad prognostic factor [11,12]. In a latest meta-analysis including 15 researches in diabetic individuals, cardiac autonomic neuropathy established an appreciable association with mortality when abnormal values of two or more indices of HRV expressed autonomic imbalance. Diabetes is known to reduce HR variability. Variations in HRV had been observed in different studies on diabetic patients among different populations based on the variations in their autonomy.In diabetic individuals with associated neuropathy, decreased value of SDNN appears to bear negative prognostic value and herald the manifestation of autonomic neuropathy. The mechanism of diabetic neuropathy is not very comprehensible, although it might be correlated to the disturbance of metabolism and autonomic nerves malnutrition [13]. In our study Non-Linear Variables andSD2werereduced inpatientswithdiabetes Mellitus compared to normal control but was not statisticallyy significant. Thereason could be small sample size. Study should berepeated in large sample size involving various complications like ischemia and foot ulcers to name a few.

Conclusion

TIPNN50 medomain Variables namely Average RR,SDRR, SDARR, RMSSD and (%) and Frequency domain variables, High frequency (HF) power, Low frequency (LF) power and Very Low frequency (LF) power

Non-Linear Variables'andSD2 were reduced in patient swith diabetes Mellitus compared to normal control but was not statisticallyy significant. Thereason could be small sample size. Study should be repeated in large sample size

Ethical Clearance- Taken from Vydehi Institutional Ethics Committee (VIEC)

Source of Funding- Self

Conflict of Interest - Nil

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Article Review: Present Perspectives of Hyperthyroidism During Pregnancy

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Abstract

Graves' disease causes inflammatory hyperthyroidism in around 80% of hyperthyroidism cases in women of reproductive age. The hormonal changes in the maternal immune system after birth may be linked to the production and expression of diabetes other than gestational and early-onset diabetes. As a result, in addition to hormonal influences, other anatomical modifications or abnormalities seen in the body during pregnancy will affect the pregnancy test. Thyroid hormones are critical for a woman's health and the commencement of her pregnancy. These hormones are essential for early development and play a crucial role in the fetus's continued growth after conception. Women with untreated or improperly controlled hyperthyroidism are more likely to have complications during pregnancy. Future diseases, particularly those that produce a large number of fetuses due to IUGRTH. The treatment of hyperthyroid pregnant women is extremely difficult, and medical staff engagement is required to guarantee that it is properly monitored and treated. Anti-thyroid drugs are commonly administered to pregnant women, and it is the medication of choice for the majority of them (ATDs). Despite the fact that both of these drugs are passed through the mother's bloodstream to the fetus, they are highly effective in the treatment of maternal hyperthyroidism. Nonetheless, they must exercise caution throughout the second half of pregnancy due to the risk of fetopathy. The most common side effect, except in the first trimesters from weeks 6 to 10, is fetal abnormalities; even with that proviso, the incidence of birth malformations is significant during the first trimester with the use of ATDs. The management of hyperthyroidism during pregnancy is divided into four areas that obstetricians are currently concerned about: Its aetiology, occurrence, correct identification, under treatment, complications, and actual or missed diagnosis and intervention, and lastly, the technique of dealing with the problem are all factors to consider.

Keywords: *hyperthyroidism, disease occurrence, diagnosis, aetiology.*

Introduction

In contrast to the thyroid-hypothyroidism, hyperthyroidism is associated with abnormally elevated amounts of thyroid hormone resulting from an enhanced production and secretion. In contrast, "hyperthyroidism" describes an excessive output [1], whereas "hypothyroid" describes elevated thyroid hormone synthesis. Basing the care of those with hyperthyroidism on experience and evidence, what has been seen in prior studies is necessary to guarantee a minimises its effects and complications. Women of reproductive age who are or who may become pregnant face the following challenges: a greater risk of hyperthyroidism, or than younger women who are

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not, for the following reasons:

1) An aetiology and prevalence of overt or suspicious hyperthyroidism in pregnancy,

2) In the first trimester, the condition of hyperthyroidism is "abnormal or high thyroid stimulating hormone in the mother and the baby",

3) Without treatment, there can be symptoms of overt hypothyroidism as well as well as hyperthyroidism throughout breastfeeding,

4) In addition to seeing an increase in TSH levels during breastfeeding, treating overt hyperthyroidism is often increases the risk of miscarriage.

Increasing amounts the hormonal modifications in pregnancy complicate the understanding of thyroid tests and the results. While explicit (the presence of all three thyroid hormones, not just one) thyroid stimulating hormone (TSH) and elevated T3 (or T4) levels[2] are common in euthyroid conditions (suppressed TSH and normal T3 and T4). Increase the study here considers how overt hyperthyroidism in pregnant women is typically is dealt with and recent thoughts on treating it.

Hyperthyroidism during Pregnancy: Aetiology and Prevalence

Etiology of the thyroid disease

Particular hyperthyroidism exists, and three distinct subtypes are Graves' disorder, multimonitor nodular, and single toxic adenoma. Many forms of hyperthyroidism present have a striking predominance of females. Still, there is a notable difference concerning the peak age of onset and how many of them there are compared to the other types (Figure 1). People with new-based, family-oriented classification and person subclassification for Graves' disease discovered that the new variant had a gradual occurrence up to a maximum age of 40 years[3]. Which was stable from the individual to family sub classification, with the inclusion, before it became an overt form of hyperthyroid Graves' disease (Figure 1) and (toxic multinodiono cellular and solitary carcinoma were seldom seen in children and were more common in older individuals. These diseases increased in frequency specifically for toxic nodular goitre was more common, with age, as is typical of tox (adnexusedl) multunoide syndromes in older adults.

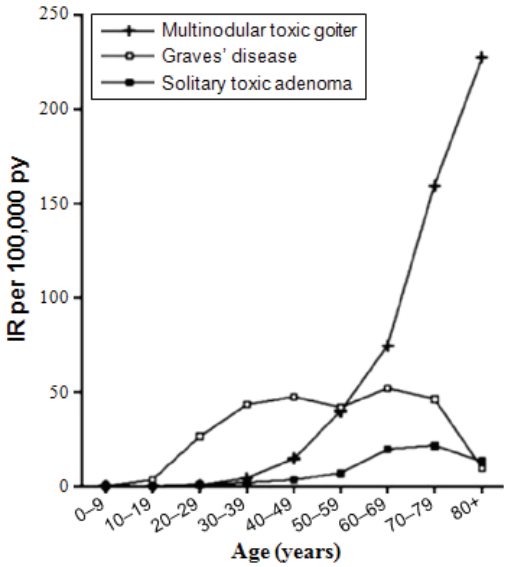

Figure 1: For the most popular forms of hyperthyroidism in Iraq, age-specific IR per 100,000 py

Graves' disease is an infectious disorder in which the thyroid gland is targeted by autoantibodies and has an elevated thyroid hormone production. In all cases (95% of those) have abnormal thyroid stimulating antibodies (TRA) in the blood, the condition caused by an overactive pituitary gland called hyperthyroidism[4]. More than one nodule can be found in a woman's thyroid gland, and no autonomous hyperthyroidism usually do not result. However, autoimmune hyperthyroidism, there is a condition where thyroid hormone synthesis occurs independently of TSH. It's also assumed that low iodine is usually causing such an enlargement of the thyroid gland later in life.

Hyperthyroidism in pregnancy: what is the rate of occurrence?

Any pregnant women with Graves' disease would go on to the ER after their thyroid has been examined, and this is the key kind of hyperthyroidism the gets overt. Though, other kinds of thyrotoxic states can be discovered in the first trimester of pregnancy and must be differentiated from the hyperthyroidism found in Graves' disease[5]. Thoroughly entangled physiological shifts in the pregnant effect on the thyroid during the early stages of pregnancy, there is a dramatic rise in human chorionic growth hormone (hCG), leading to a surge in thyroid hormone levels. The hCG is a glycoprotein synthesised in the placenta, which influences the TSH receptor because of structural similarity. Gestational hyperthyroidism is a non-autoimmune condition that often lasts in the first trimester of pregnancy and is attributed to high levels of human chorionic gonadotropin. In gestational hyperthyroid, the more common Graves' disease is often manifested[6] as hyperemesis gravidus, although it is impossible to tell apart from hyperemesis syndrome in certain cases. As tested by a radioactive dye, the existence of TRAb confirms the "diagnosis of Graves' disease".

Expand the prevalence of "Graves' disease" may be increased before and after birth. One of the two dominant functions of pregnancy is the profound immunologic improvements in the maternal system, which often appear to increase TSH levels. A particularly high amount of oestrogen makes thyroid hormone output go up, leading to a spike in total T3 and total T4.

Furthermore, it is essential to follow certain hormonal modifications while attempting to determine the serum hormone concentrations of pregnant people. There is a significant increase of thyroxine-binding globulin content during breastfeeding, resulting in free thyroid suppression. An immune recovery then accompanies this after the baby is born[7]. Since these gene mutations affect the initiation of autoimmunity, they might cause damage to an individual's immune system (Figure 2). What was discovered in a Danish cohort of 403,958 women's total populations (reported in medical literature as temporary hyperthyroidism or thyroiditis) turned out to be the case that women suffered from the condition early in pregnancy experienced incremental changes and continued worsening. Those who survived that time had given birth were more susceptible to its after giving birth, presumably because the population is no longer immune to the disorder[8], as we assume (Figure 2). It is possible that individuals predisposed to Graves' disease could be driven by hCG-triggered increases in the output of thyroid hormone during the early stages of pregnancy. However, Graves' disease that occurred before conception could become more complicated in the early stages of pregnancy.

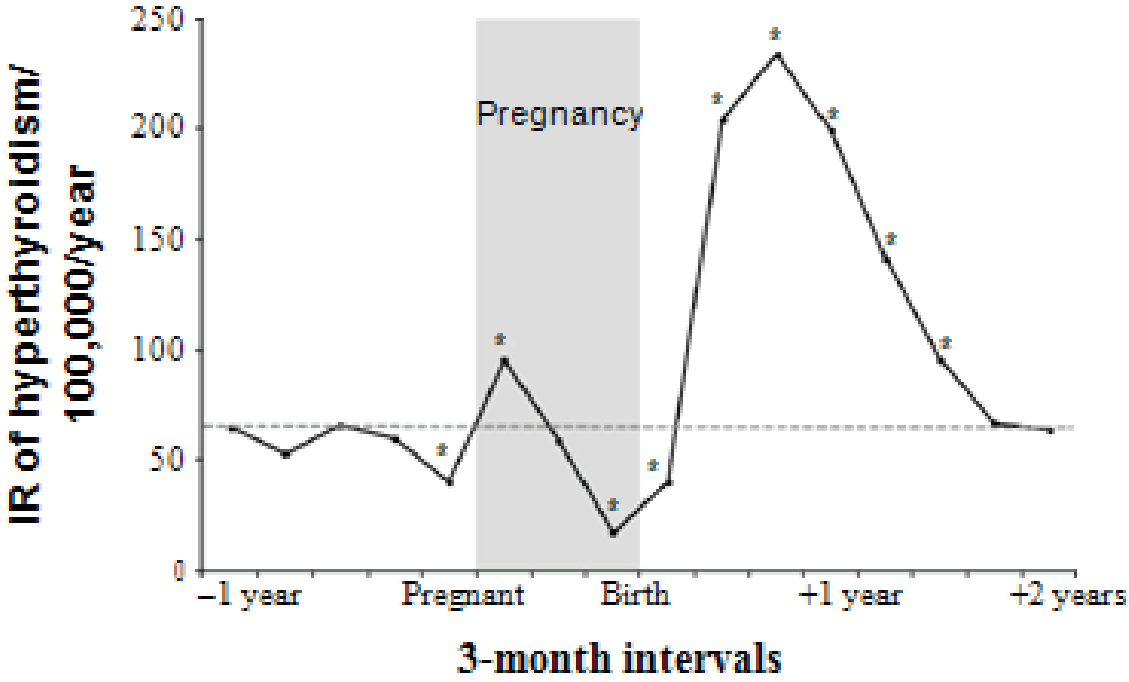

Figure 2: A live-birth child is born at three months before and during the first pregnancy after IR of maternal hyperthyroidism.

Abbreviation: IR, incidence rate.

Pregnancy has an increased risk of hyperthyroidism

Disruption due to a change in thyroid hormone levels

As the physician may evaluate for apparent hyperthyroidism by checking a suppressed TSH and elevated T3 and T4 levels, the underlying condition is hyperthyroidism. On the other hand, new travel sizes, the physiological changes that take place during pregnancy can interfere with the perception of thyroid tests[9]. An increase of thyroxine levels is another way the body adapts to elevated levels of hCG in the early stages of pregnancy by producing more thyroid hormone and suppressing the TSH. The form-3-deiodinase enzyme, which is used to type and research placental hormone synthesis in many countries, is also elevated in the placenta[10-11]. The use of ultrafiltration or dialysis for the initial calculation of free thyroid hormone concentrations is technically complicated. However, it can be done using protein precipitation or chemical treatments to separate the protein-bound component. While in routine analyses, the assays are used. The researchers use indirect measures that estimate total hormone concentration to quantify free hormone, not just the free hormone measures. In addition, techniques used to calculate free thyroid hormone concentrations vary greatly.

It is also important to consider that a woman's thyroid function will vary with each pregnancy. During the first and last trimesters have been suggested, particularly those targeting the second and third trimesters. Expand; However, it might be inaccurate to say that there are little physiological improvements in the first trimester of pregnancy, as this term might be insufficient to fully capture all that is taking place[12]. During early pregnancy, the Dimension Vista assay (Eschborn, Germany) shows lower and upper limits of thyroid stimulating

hormone (TSH) concentrations (measured as in Figure 3) which were matched to healthy Danish women, respectively. When does a non pregenergetic fluid not constitute true nutrition? This information is provided by the producer, which is highlighted with dotted horizontal lines. In adults without pregnancy, a diagnosis of hyperthyroidism will be provided if the TSH level was lower than 0.358 mU/L whereas the fT level was higher than 18 pmol/L. The study demonstrated that, as shown in Figure 3, the overt hyperthyroid classification criteria did not correctly identify all pregnant people[13]. The lower reference limit for Thyroid Stimulating Hormone was higher in early pregnancy and subsequently lower in the second trimester. Whereas for people who are not pregnant, the upper reference level was less variable, but with more prominent later in pregnancy, for an increasing variation of 0–14 weeks, the lower reference level in the narrowing earlier on the scale was consistent from week 9 to week 12. Preferably, these are set as week-specific ranges during the first trimester to account for changes in the thyroid during this period of pregnancy.

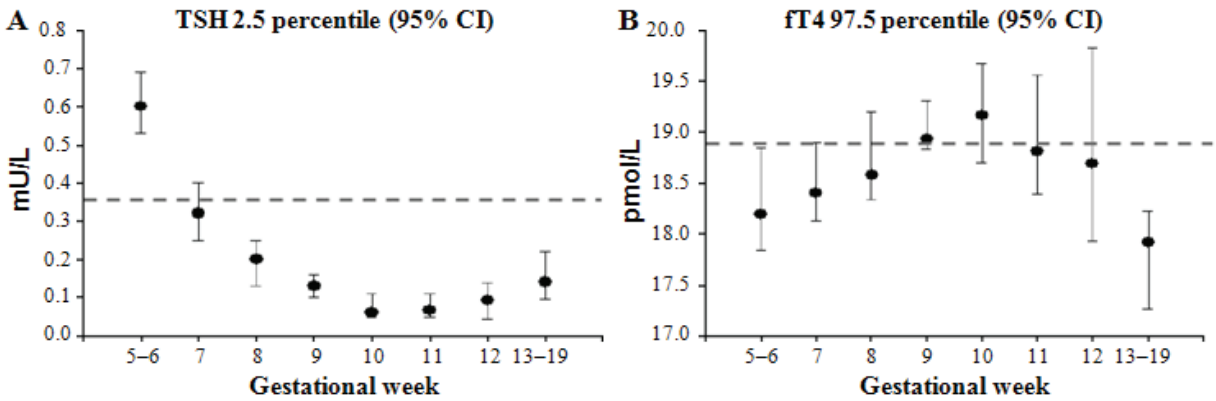

Figure 3: The diagnosis of hyperthyroidism in early pregnancy for the automatic immunoassay Dimension Vista (Siemens) was used to establish reference limits.

Pregnancy-related untreated hyperthyroidism

Unassisted reproduction

Delaying the diagnosis of hyperthyroidism in pregnant women can cause many issues, such as the dangers of fetal development, maternal and neon-pregnancy health. A type of overt hyperthyroidism is recognised as a serious clinical issue[14]. Laboratory and control measures implemented Expand While the relationship between subclinical hyperthyroidism and pregnancy problems has not been established, research has not uncovered it either.

Thyroid hormones are essential for the growth of the fetal during gestation. Normal levels of thyroid hormone are required during pregnancy in the mother and during delivery, which results in the normal levels of thyroid receptor function in the fetal. Hypothyroidism can raise the risk of early and late pregnancy failure. There is a connection between maternal hyperthyroidism and early childbirth and an increased chance of delivering[15] underweight infants, and m is of adverse effects for the female pregnancy, such as preterm labour and preeclampsia and ea syndrome biliary or maternal heart failure.

Your fetal already has thyrotropic hormone receptors in the fetal brain, and these help determine the function of the neurological system of the unborn child. But during the second half of birth, the fetal

thyroid gland's capacity to produce thyroid hormones expands. Thyroid production increases somewhat in the second half of the pregnancy, but the fetal is more critical for the second half[16]. Experimental data on high levels of maternal hormone disrupt normal brain function in the fetus, which was proven in the general community. As well as in an estimated one group, have shown Heller's research also shown out in epidemiological trials that an excess of maternal thyroid hormone is correlated with brain growth problems in the infant.

The risks of both hyperthyroidism and attention deficit hyperactivity disorder and later in life and undetected thyroid hormone levels during pregnancy is elevated in the children of children whose mothers were first diagnosed with hyperthyroidism during pregnancy (having never had any previous medical treatment) were shown in a national Danish survey to be greatest in that group (this is one that first-time treatment with medical treatment and, presumably, pregnancy). It is suggested that the fetus's thyroid conditions[17] can result in subtle, systemic, or functional alterations throughout the development of the early fetal brain development may have a lasting impact on the adult disease status 27 The existing theory doesn't provide for much more research, so further experiments, including studies measuring the maternal thyroid gland during pregnancy, are required to establish the relationship between thyroid function and pregnancy.

Cure of Hyperthyroidism during Pregnancy

Premature pregnancy

To avoid maternal and infant risks, overt hyperthyroidism should be properly handled. Physiological hCG symptoms may increase at the level but there needs to be no attempt to treat those before 12-15 weeks gestation, since it is more likely than the other forms of hyperthyroidism (ATDs). There is no evidence that treating this acute physiologic hyperthyroidism with any TCD treatment can improve the chance of a successful pregnancy. The infant was treated for (via a course of diet and rehydration) and tested (every two to three weeks) for excessive thirst in order to provide[18] an accurate assessment of thyroid activity every two to three weeks over the course of their care.

ATD is the preferred therapy for overt hyperthyroidism in pregnant people. 5 Pregnancy cannot be treated with radioiodine. Thyroidectomy, ideally in the second trimester of pregnancy, is an alternative therapy if ATDs are not accepted.

Thioamides are substances that block the thyroid gland from developing thyroid hormone from being produced[19-20]. Several of the medications available include methiomylmerchloride (Methimazol), propylamine, and the prodrugs CMZ, MMI, and propylthazin, respectively (PTU). Research suggests that the drugs work in comparable ways as treating hyperthyroidism. By their full development into the foetus, they all occupy the placenta, leading to hypothyroidism in late pregnancy (see the segment on "Late pregnancy"). However, the main issue when using these medications in early infancy is the possibility of birth defects.

Before the pregnancy, it was discovered that the exposure to At doses during the first three trimesters of the pregnancy was connected with birth defects[21], Eleven of the two of the eleven moms who had given birth to a child with a birth defect on the scalp were helped to increase their birth weight with MMI, according to a research done in a 2014. In addition, two further instances of birth defects were discovered in babies born to mothers who were administered MMI or CMZ while pregnant[22-23]. airway of delivery with cleft lip and oesophagus, oesophagus, and upperair delivery defects, as well as other malformations is considered to be components of the population

syndromes, and so resulted in the discovery of a community complex OME, pyloric septal and duodisc and GI tracts[24], and oesophagus with cleft duodental and pyloric duodental intral CoAte, pylor orupperways distribution defects, as well. since the 1990s, results from clinic and population-based studies have confirmed the apparent risk of birth defects seen in these latest clinical research studies Japan and Iraq have conducted studies finding that indicate that MMI/CM causes high-affected children to have an increased risk of malformations in pregnancy[25]. Additionally, the birth defects affected different organ systems, as seen in the upper panel of Figure 4, were found to be related to environmental factors. The embryopathy previously described may also (besides) show up in the general population; it is supported by a few of these studies as well.

Additionally, a Danish research demonstrated that babies who were treated with PTH had an increased likelihood of congenital abnormalities [26]. While the types of birth defects following methotrexatehinamide and zincirodate exposure were similar, the type of birth defects found in these two examples was distinctly different and less harmful (Figure 4). Along with the a preauricular sinus, kidney defect, sacral groove, and nephropsydrops, there were discovered in the face and back, as well as the urinary tract disorders [27-28]. More than two-thirds of cases have been treated surgically, with respect to their seriousness of their illness.

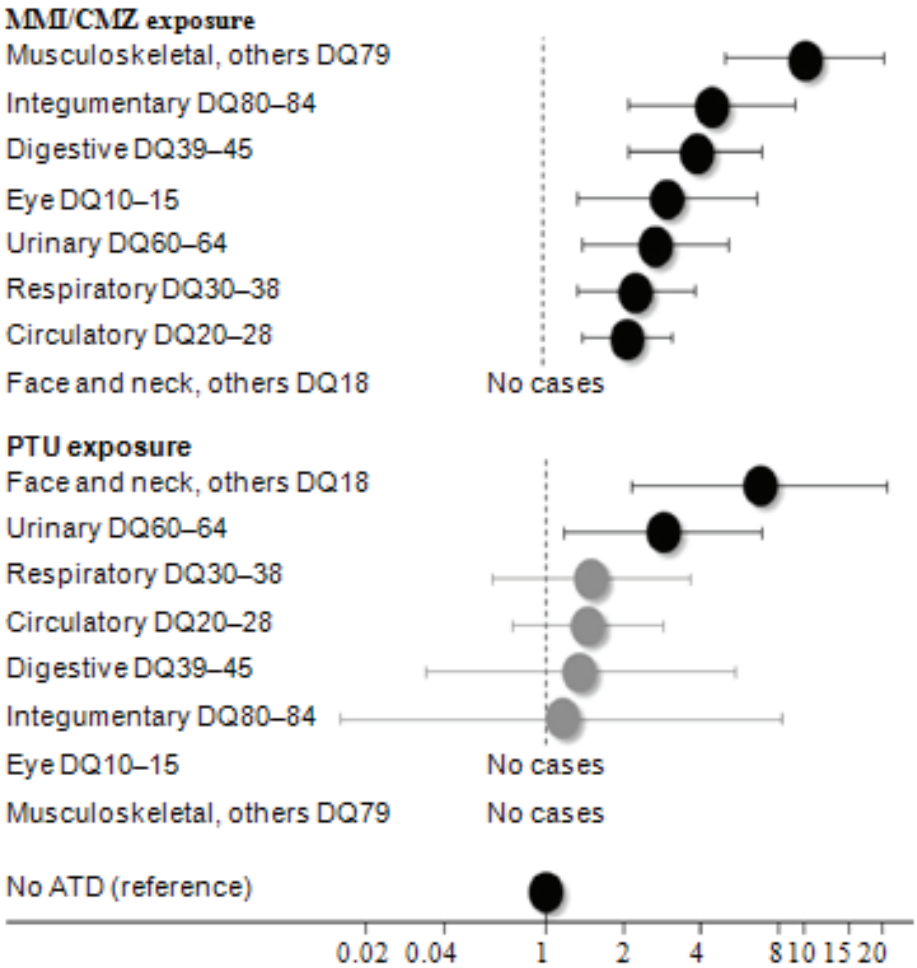

Figure 4: In 1,097 infants, an adjusted OR with a 95% confidence interval was found for subtypes with congenital disabilities.

Due to the possibility of birth defects, current foreign guidelines warn against utilising PTU in the first trimester of pregnancy, and MMI can be prevented[29] because it may occur if PTU is used; instead, if PTU is used in the first trimester, the suggestion is that it should not be moved to another class of anticonvulsants until after first trimester to prevent liver toxicity.

As PTU has been the third most often cited[30] as a leading cause of liver transplantation in the U.S., the onset of liver disease when on the PTU regimen has been of this complication to take note of. However, a new Danish population-based survey confirmed the observation, which found that the incidence of adverse drug reactions was also increased for those using these medications in pregnancy[31]. Agranulocytosis and liver disease were very uncommon during infancy, with birth defects being the most common complication.

Table 1: Women who are or expect to become pregnant are most often advised to limit their use of thyroxine because of the danger of hyperthyroidism.

	Planned pregnancy
1	The MMI to PTU transfer ratio is 1:20, so 200 mg PTU per day substitutes 10 mg MMI (or 15 mg CMZ).
2	Women who are receiving ATD care should tell their doctor whether they are considering a baby.
3	When a pregnancy is expected, care may be switched to PTU before the baby is born, particularly in younger people with daily periods.
4	There's a good chance of pregnancy.
	Detected pregnancy
1	If ATD therapy is not needed, weekly thyroid function monitoring should be done during the first trimester of pregnancy.
2	The liable practitioner should assess if ATD care is necessary.
3	Once a pregnancy is discovered, the patient can call her doctor right away to determine whether her existing ATD medication can be extended, modified, or discontinued.
4	If conception is a concern, women receiving ATD care should take a pregnancy test on the first days after a missed menstrual cycle.
5	MMI/CMZ or PTU may be used if care is required during the first trimester of pregnancy.
6	Women who are being treated for ATD should be told to diagnose pregnancy as soon as possible.
7	PTU can be used if ATD therapy is needed during the first trimester of pregnancy.

More research is required in this area, including experiments on alternative treatments to ATD during pregnancy. The latest proposals for treating overt hyperthyroidism in early pregnancy are summarised in Table 1. ATD toxicity and the possibility of birth defects are more prevalent between weeks 6 to 10 of pregnancy[32]. The proposals include a discussion of potential pregnancy for a woman who might become pregnant, as well as a plan for detecting pregnancy as early as possible. When pregnancy is suspected, the responsible practitioner needs to evaluate the therapeutic indications for continuing ATD care[33]. Thyroid function test findings, TRAb measurements, present dosage and length of ATD therapy, and clinical effects should also be included in this assessment.

In the latter stages of conception

Her nodular type of hyperthyroidism also needs to be considered when developing treatment strategies for fetus in the late pregnancy stage. Graves' hyperthyroidism is a source is present in the mother's blood in the latter stages of pregnancy and in these MUTagens, which cross the placental membrane and result in high levels of MUT is present in the fetal'[34]. Thus, an increase in thyroid receptor activity may also cause increased production of thyroid hormones in the fetal gland. Foetal hyperthyroidism can arise during the second half of pregnancy because the fetal thyroid gland has the capacity to produce thyroid hormones during this period[35]. As previously stated, all currently approved antithyroid treatments would benefit from increasing the supply of the mother's ATD supply when helping with the treatment of hyperthyroidism during pregnancy. On the other hand, there is a chance of fetal hypothyroidism if one undergoes certain therapy, according to Shakespeare induction[36]. The thyroid's autoimmunity seems to moderate in the context of increased levels of maternal hypothyroidism during the later stages of pregnancy (Figure 2). 10 When the mother is euthyroid, ATD is no longer used to euthyroidify the fetal.

Block replacement can be used in women who are not yet pregnant or in their first trimester to treat goiter[37]. Expand this approach is designed to use ATD as an overdosage of thyroid hormone supplementation to induce euthyroidism. Still, normalization of the thyroid levels during therapy will prevent the overtreatment of hyperthyroidism. Do not use the administration of high dosages of AT in pregnant people since they can do more harm than good. Folate, an iodine-enriched food[38], may be added to improve the newborn's capacity to make thyroid hormone levels to not overtreat the fetus and mitigate the risks of overtreatment. Expand this regimen is good in unique situations such as fetal thyrotoxicosis, though, where there is no other source of thyrotoxicosis that needs to be treated. TRAb in the woman is considered the risk of developing fetal hyperthyroidism. A consequence of prior care for Graves' disease may be ruled out[39]. The fetus may be described as anemic, subsequently enlarge, and decompensated. If the woman has increased levels of ATD may think instead of TTH, then AT treatment will cure her, and if the levels do not return to normal once the baby is born, she will remain euthyroid[40-41]. Although such fetal thyrotoxicosis usually occurs during the early stages of pregnancy, it can be identified by maternal urine trabanditrophin levels[42]. Mid-pregnancy (first trimester) should be considered in the presence of an increase in the TRAb levels if TRAb levels continue to rise, further biochemically and clinically should be followed by the third diosmin. Wasserman Lupoeting about week 20 weeks and again a plan developed in the third trimester if they have not returned to normal by week 30[43-44]. Because late pregnancy includes the baby's risk of hyperthyroidism, it is essential to also talk about how hyperthyroidism increases the risk.

Such was the case with the rule after the birth of newborns whose mothers have unresolved

hyperthyroidism or prior thyroid ablation[45-46]. The newborns had neonatal hyperthyroidism with Graves' disease, or it had the hyperthyroid disease during gestation and is either on the mother's thyroid gland. Delayed neonatal hyperthyroid is diagnosed in children is far more common in those exposed to ATD during pregnancy, both during pregnancy and birth. TRAb (uses as much less than 50% of total thyroxine clearance) vanishes shortly after birth, while neo tenyrosis (a condition in which use of all total thyroxine exceeds 50% of total body clearance) can persist in the newborn for many days[47-48]. Concerning your child's chance of having a problem with hyperthyroidism in the newborn period, the amounts of maternal tralog TTHb at the time of delivery may be used to make an estimate. It is advised in those that have more than three times the normal TRAb thresholds[49] to give ultrasounds for an ultrasound of fetal development, an ultrasound for detecting fetal goitre, and an ultrasound for the fetus's heart rate.

Discussion

Graves' syndrome is the most frequent source of any of the autoimmune hyperthyroidism in pregnancy. Around 0.5% of births have been observed to end in spontaneous miscarriage, according to various sources[50]. At present, it is not established if this is the first appearance of the condition or whether it occurs during a prior course of hyperthyroidism or whether that the medications are administered during antithyroid therapy, a patient may present as a Chronic expanded definition: Hyperthyroidism (as well as hyperthyroidism) may be the result of hormone related to heart disease[51]. hyperthyroidism caused by other unusual conditions, nonendemic diseases such as MEN, TAA, and factitious hyperthyroidism more common than Graves' disease as the source of hyperthyroidism is gestational thyrotoxicosis or hyperemesis gravish/transient thyrotoxic mole (with hyperemesis in the third trimester), which is present in around 3–5 percent of births, with several pregnancies, and hydatiform mole, which involves those that are pregnant[52-53] and those who are suffering from the conditions caused by it.

Whereas, autoimmune disorders often increase their behaviour during the first trimesters and then go back to normal levels, such as after birth, in Graves' disease the pattern of activity is inverted, meaning that an increased activity occurs during the second trimester of pregnancy and decreases afterwards[54].

Since the majority of the signs of hyperthyroidism show up in those whoopingradonas tremor, wet skin, and an increased heartbeat can be common in regular pregnancy, most of those things are likely to be normal[55-56]. Early in pregnancy, the level of thyroid-thyroxine-triiod (T-4) and thyroid-stimulating hormone (TSH) levels may normalise (e) from an estrogen-induced rise and decreasing levels of thyroxine-triiodin, which are tied to the production of thyrotropoecina (TSH), may obscure signs of maternal[57] hyperthyroidism [thyroid- TT4].

There are particular factors that must be taken into account in managing hyperthyroidism during breastfeeding, so the health of the woman, the child, and the newborn could be impacted.

Where untreated or poorly treated maternal hyperthyroidism results in a termination of pregnancy, particularly preeclamps, intrauterine growth restriction, fetales in utero[58], and early birth, and infants that are small for their gestational age, they have an abnormal amount of weight gain. Often, there are issues like congestive heart failure, postpartum bleeding, and postpartum cardiovascular collapse[59-60]. Excessive antithyroid medication taken in the early pregnancy and its effect on fetales may be either hypothyroid or the crossing of the placenta (exposure of the fetal to antithyroid medications)[61-62]. Clinical disorders that occur as the more often you

go below the reference level of thyroid stimulating hormone (FT4-4 or T-4) are more effective when you don't hit the upper limits on the normal number of changes (3 times a day per day). Additionally, mothers who have been infected with HIV during pregnancy can give birth to or transmit TRAb in the newborn[63-64], resulting in fetal or neonatal Graves's disease Central hypothyroidism, which is generally seen during pregnancy with normal serum thyroxine levels, results from higher levels of thyroxine in the mother than in the fetal if the mother's thyroxine levels aren't controlled.

The condition known as postpartum thyroid exposure or Graves' disease in which the mother develops after giving birth may be managed with postpartum[65] radioiodine therapy but it must be followed with whole body radiologic testing. Antithroid medications are typically used to cure Graves' disease because of their ability to normalise the thyroid-stimulating hormone levels[66-67]. While preliminary studies have shown that there are no PTUHT (from 150 to 300 mg/day) or 30 mg/day doses with PTU of no significant effects on thyroid function or physical growth[68] in T-suppressed infants with lactating thyrotoxic mothers, long-fed babies seem to benefit from more, However, the choice of opiate during childbirth is strongly advised against, because of the risk of damaging the liver in either the mother or the infant.

Strictly monitoring of hyperthyroidism is essential to provide the woman and her child the best treatment and to ensure that she doesn't develop the condition, and also to avert any negative effects on her and the developing fetal, as well as the baby[69-70]. It was found that although there was no dispute among the American Association of Clinical Endocrinologists, the Endocrinologists, and the American Thyroid Association on the fact of diagnosis and care of hyperthyroidism in pregnancy, there was debate about which issues should be addressed. Almost all of the detail can be included in the document or advice. If the writers of both deserve commendation for synthesising nuanced evidence[71] into high-quality recommendations, however separate guidelines, it can confuse clinicians as to choose which to follow. In the authors' view, all of these policies may be seen as effective and up-to-date treatment of toxic Thyrotoxic women can experience two alternatives: either treat themselves or treat their physician/maternal healthcare provider first.

Upcoming Perspectives

A pregnant woman's hyperthyroidism is a very serious medical problem, biological, and psychiatric condition that must be acknowledged by those concerned. There are still considerable risks to both maternal and fetal health that the illness must be well handled and well to ensure symptoms do not occur with one of both[72-73]. Untreated maternal thyrotoxicosis may influence disease during gestation may put the fetus on the path to the diseases it is sure to follow for life, and future research may look at fetal thyrotoxicosis.

Hippotherapy for people includes various practitioners (such as a general physician, obstetrician, and endocrinologist) for different stages[74] in the female reproductive life. However, the context has changed since the first time this was established. An ongoing issue in the management of hyperthyroidism has been controversial since its discovery includes the possibility of determining the presence of early pregnancy and the severity of the condition. Studies in early pregnancy that could usefully address the week-to-week difference in thyroid function are required[75]. Furthermore, existing therapies and risks and risks associated with the available ATDs should be investigated, and the likelihood of discovering alternative ATDs with less and less serious side effects.

Ethics approval and consent to participate

The work is a review; the authors didn't need to perform experimental and clinical work.

Consent for publication

The manuscript didn't contain any individual person's data.

Competing Interests: No conflict of interests

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Author's contributions

All authors in this review article were drafted and approved the manuscript

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