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Correction of metabolic factors increases pregnancy rate in sub-fertility patients

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Abstract
Background: Infertility, affecting 8–12% of reproductive-age couples globally, is often exacerbated by metabolic abnormalities such as insulin resistance, dyslipidemia, thyroid dysfunction, and hyperprolactinemia. These factors disrupt hormonal balance, impair ovulation, and reduce pregnancy success rates, particularly in sub-fertile women.
Aim of the study: To investigate the impact of correcting metabolic dysfunctions on ovulation and pregnancy rates in sub-fertile women.
Methods: This prospective analytical study was conducted at the Department of Obstetrics and Gynaecology, Khulna Medical College and two others Private Hospitals, Khulna, Bangladesh over three years, from January 2021 to December 2023. A total of 120 sub-fertile women aged 18–45 years were included. Baseline and follow-up assessments of metabolic parameters—BMI, blood glucose, lipid profile, thyroid function, and serum prolactin—were performed, with targeted interventions implemented to address abnormalities. Ovulatory function was monitored after three and six menstrual cycles. Data analysis was conducted using SPSS, with $p<0.05$ considered statistically significant.
Result: The intervention significantly improved metabolic and hormonal parameters. Mean TSH levels decreased from 7.42±2.09 to 3.12±1.05 mIU/L ($p<0.001$), and serum prolactin levels dropped from 25.36±5.24 to 14.82±4.09 ng/mL ($p<0.001$). Estradiol levels increased to 52.89±13.27 pg/mL ($p<0.05$), and progesterone rose to 5.62±1.21 ng/mL ($p<0.001$). Ovulation was achieved in 66.67% of participants within three cycles and 8.33% within six cycles, demonstrating a marked improvement in reproductive outcomes.
Conclusion: Metabolic correction plays a pivotal role in improving ovulatory function and pregnancy rates in sub-fertile women. Addressing metabolic dysfunctions through targeted interventions should be an integral component of fertility management, offering promising outcomes for women seeking to conceive.

Keywords: Sub-fertility, metabolic correction, hormonal balance, ovulation improvement, pregnancy outcomes

Introduction
Infertility is a growing social problem. Although infertility is defined as the inability to conceive despite 12 months of regular sexual intercourse with the intention of having a child in women <35 years of age (American Society for Reproductive Medicine—ASRM), often a term of 6 months of unsuccessful attempts in women >35 years of age is applied in clinical practice within the similar diagnostic management [1]. It is difficult to estimate the sheer scale of the phenomenon and the count of couples of reproductive ages in the world struggling with infertility is presented as between 8–12% and even as much as 18%. Most of these are from developing countries [2, 3]. The Central and Eastern region, Central and South Asia, and Sub-Saharan Africa have the highest rates of infertility, reaching up to 30% [4]. Subfertility is used generally to name any form or grade of reduced fertility in couples unsuccessfully trying to conceive [5]. It affects 15% of reproductive-age couples. About 70 million couples experience subfertility worldwide [6]. The relationship between metabolic factors and fertility is a complex interplay that influences reproductive health in both men and women. Various metabolic disorders can significantly affect fertility. Three major interrelated abnormalities characterize metabolic syndrome: elevated blood pressure, dyslipidemia, and elevated blood plasma glucose [7]. The three abnormalities directly contribute to pro-inflammatory and prothrombotic state, an outcome that predisposes an individual to the development of diabetes type 2 and atherosclerotic cardiovascular disease [8]. Insulin resistance and hyperinsulinemia are the primary underlying metabolic abnormalities reported in metabolic syndrome and polycystic ovarian syndrome [9].

Elevated circulating insulin levels and insulin resistance induces unfavorable changes in increased androgen production and lipid metabolism from theca cells [10]. Having excess release of androgens can result in unfavorable metabolic problems resulting in central distribution of fat and dyslipidemia. Dyslipidemia and excess insulin in obese women may contribute to metabolic syndrome and polycystic ovarian syndrome [7]. The android fat distribution pattern may be explained by hyperandrogenism, resulting in a vicious circle of central adiposity, hyperinsulinism, and metabolic abnormalities [7]. Thyroid hormone is indispensable for normal development and metabolism of most cells and tissues [11]. The thyroid hormones also affect the female reproductive organs. Overt hyperthyroidism results in the alteration of estradiol metabolism and the augmentation of gonadotropin in response to gonadotropin-releasing hormone. Baseline gonadotropin concentrations are also frequently elevated [12]. The prevalence of primary or secondary infertility associated with hyperthyroidism has been described to be 0.9% to 5.8% [13, 14]. Hypothyroidism has been associated with altered ovulatory function, menstrual irregularities, subfertility, and higher (recurrent) miscarriage rates. Also, hyperprolactinemia has been associated with altered ovulatory function, menstrual irregularities, subfertility, and higher (recurrent) miscarriage rates. Subclinical hypothyroidism (SCH) is defined by an increase in serum thyroid-stimulating hormone (TSH) concentrations with normal free thyroxine (FT4) levels. The prevalence of SCH in subfertile women has been reported to vary from 0.7% to 43% [12]. In recent years, researchers have been looking for lifestyle factors that favor fertility. One of them is a properly balanced diet. Nutrition can have a negative or positive effect on the fertility of both women and men and the impact depends on both quantitative and qualitative properties of the diet, such as the caloric content of each macronutrient (carbohydrates, fat, and protein), as well as the specific acid profiles fatty acids, proteins, and carbohydrates. All components of nutrition constitute a dietary pattern [15]. A well-balanced diet with a low glycemic index, with the lowest possible proportion of processed foods, seems to have a positive effect on fertility.

The study aimed to investigate the impact of correcting metabolic dysfunctions on ovulation and pregnancy outcomes in sub-fertile women.

Methodology & Materials

This prospective analytical study took place in the Department of Obstetrics and Gynecology, Khulna Medical College and two others Private Hospitals, Khulna, Bangladesh. The study spanned three years from January 2021 to December 2023. Patients were chosen through purposive sampling based on specific inclusion and exclusion criteria. The study included 120 sub-fertile female patients.

Inclusion criteria

Female participants aged 18–45 years with sub-fertility information were included in this study.

Exclusion criteria

The study excluded female participants with a history of hysterectomy, or bilateral oophorectomy. After outlining the study's aims, objectives, and procedures, written informed consent was secured from each participant. Baseline demographic information of the patients was subsequently recorded, with all data being kept strictly confidential. Ethical approval for the study was granted by the institutional ethics committee. The study examined metabolic factors such as Body Mass Index (BMI), blood glucose level, lipid profile, thyroid function, and serum prolactin. Thyroid and prolactin function were assessed both at baseline and again after 3 months. Ovulation status was monitored following 3 and 6 menstrual cycles.

BMI was calculated by dividing body mass in kilograms by height in square meters. Weight and height measurements were taken by trained professionals. According to WHO guidelines, BMI classifications are as follows: normal weight (BMI: 18.5–24.9 kg/m²), overweight (BMI: 25.0–29.9 kg/m²), and obesity (BMI: ≥30 kg/m²) [16]. Blood glucose levels were determined using reducing methods, while lipid profiles were analyzed through GC-MS techniques [17]. Thyroid function was assessed via HPLC methodology. Based on the 2009 harmonized criteria for metabolic syndrome [18], participants were considered metabolically healthy if they did not exhibit any of the following four components: (1) Systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, self-reported hypertension, or use of antihypertensive medication; (2) Fasting blood glucose ≥ 100.9 mg/dL, self-reported diabetes, or use of antidiabetic medication; (3) HDL cholesterol < 23.24 mg/dL for women or use of lipid-lowering medication; and (4) Triglycerides ≥ 30.63 mg/dL or use of lipid-lowering medication. Individuals with one or more of these components were categorized as metabolically unhealthy [19]. For women, treatment to reduce thyroid-stimulating hormone (TSH) to below 2.5 mIU/L was recommended if TSH levels exceed 4.0 mIU/L. Women with thyroid autoimmunity (TAI) and TSH levels between 2.5 and 4 mIU/L was taken into account to be benefited from treatment to optimize embryo development, depending on individual circumstances [20, 21]. Mild prolactin elevations, ranging from 25-50 ng/mL, typically did not cause significant changes in menstrual cycles but estimated it might reduce overall fertility. Higher prolactin levels, between 50-100 ng/mL, was thought to lead to irregular menstrual periods and a substantial decrease in fertility [22].

Statistical Analysis

The data were systematically organized into appropriately designed tables, each accompanied by a detailed description to ensure clarity and ease of understanding. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software (version 26). Continuous variables were presented as mean±standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Comparisons of continuous variables between groups were performed using the Student's t-test, whereas categorical variables were analyzed using the Chi-square test. A *P* value of less than 0.05 was considered indicative of statistical significance.

Results

A total of 120 subjects were included in this study. The mean age of the participants was 37.21±3.21 years. Age distribution revealed that 42.50% of participants were in the 36-45 years age group, followed by 35% in the 26-35 years group, and 22.50% in the 18-25 years group. The mean BMI was 23.12±2.94 kg/m², indicating a generally healthy weight profile among the subjects. The average blood glucose level was 92.51±10.31 mg/dL.

Insulin resistance, as measured by HOMA-IR, had a mean value of 2.31±0.82, reflecting moderate insulin sensitivity. Regarding the lipid profile, the mean total cholesterol level was 190.52±30.21 mg/dL, while LDL cholesterol averaged 110.3±25.42 mg/dL. HDL cholesterol had a mean value of 55.2±15.11 mg/dL, and triglycerides showed an average of 150.41±40.62 mg/dL (Table 1). Table 2 showed that a majority, 71.21%, were classified as euthyroid, indicating normal thyroid function. Subclinical hypothyroidism was observed in 15.73% of participants, while 8.35% were diagnosed with clinical hypothyroidism. Hyperthyroidism was the least common, affecting 4.71% of the study population. The biochemical examination of thyroid function for the subjects revealed significant improvements over three months. The mean TSH level decreased from 7.42±2.09 mIU/L at baseline to 3.12±1.05 mIU/L after three months, demonstrating a highly significant reduction (p<0.001). Similarly, free T4 levels showed a significant decrease from 17.82±3.13 micromoles/L to 14.08±2.95 micromoles/L (p<0.05). Free T3 levels also declined significantly, from a baseline mean of 3.00±0.75 pg/mL to 2.50±0.65 pg/mL (p<0.01) (Table 3). Table 4 revealed significant hormonal improvements after three months of metabolic correction. Serum prolactin levels decreased from 25.36±5.24 ng/mL to 14.82±4.09 ng/mL (p<0.001), with reductions in LH (12.45±3.89 to 8.21±2.76 mIU/mL, p<0.05) and FSH (9.58±2.47 to 7.94±2.03 mIU/mL, p<0.05). Estradiol increased from 45.12±12.38 to 52.89±13.27 pg/mL (p<0.05), and progesterone rose significantly from 1.21±0.52 to 5.62±1.21 ng/mL (p<0.001). Assessment of ovulation status revealed that 66.67% achieved ovulation within three cycles. An additional 8.33% required up to six cycles to achieve ovulation. However, 25% of the participants required further treatment to induce ovulation (Table 5).

Table 1: Demographic characteristics of the study subjects before consultation (N=120).

Variables	Mean±SD	
	Frequency (n)	Percentage (%)
Age (years)		
18-25	27	22.50
26-35	42	35.00
36-45	51	42.50
Mean±SD	37.21±3.21	
BMI (kg/m^2)	23.12±2.94	
Blood glucose level (mg/dL)	92.51±10.31	
Insuline resistance (HOMA-IR)	2.31±0.82	
Lipid profile		
Total cholesterol (mg/dL)	190.52±30.21	
LDL cholesterol (mg/dL)	110.31±25.42	
HDL cholesterol (mg/dL)	55.21±15.11	
Triglycerides (mg/dL)	150.41±40.62	

LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein.

Table 2: Distributions of study subjects according to thyroid function (N=120).

Types of thyroid status	Frequency (n)	Percentage (%)
Euthyroid	85	71.21
Hyperthyroid	6	4.71
Subclinical hypothyroid	19	15.73
Clinical hypothyroid	10	8.35

Table 3: Comparison of the study population's Biochemical examination of thyroid function (N=120).

Thyroid function	Baseline status	After 3 months status	P-value
	Mean±SD		
TSH (mIU/L)	7.42±2.09	3.12±1.05	<0.001
Free T4 (micromole/L)	17.82±3.13	14.08±2.95	<0.05
Free T3 (pg/mL)	3.00±0.75	2.50±0.65	<0.01

TSH: Thyroid-Stimulating Hormone

Table 4: Comparison of the study population's Biochemical examination of prolactin function (N=120).

Prolactin function	Baseline status	After 3 months status	P-value
	Mean±SD		
Serum prolactin (ng/mL)	25.36±5.24	14.82±4.09	<0.001
LH (mIU/mL)	12.45±3.89	8.21±2.76	<0.05
FSH (mIU/mL)	9.58±2.47	7.94±2.03	<0.05
Estradiol (pg/mL)	45.12±12.38	52.89±13.27	<0.05
Progesterone (ng/mL)	1.21±0.52	5.62±1.21	<0.001

LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone.

Table 5: Ovulation status of the study population (N=120).

Ovulation status	Frequency (n)	Percentage (%)
Within 3 cycles	80	66.67

Within 6 cycles	10	8.33
More treatment required	30	25.00

Discussion

This study presents a detailed evaluation of the demographic characteristics, thyroid function, prolactin level, and ovulation status of women experiencing subfertility, both before and after targeted interventions aimed at addressing metabolic factors. The findings shed light on the complex interplay between metabolic health and fertility, emphasizing the potential of corrective measures in improving reproductive outcomes. The study revealed that the majority of participants were aged 36–45 years, comprising 42.50% of the total sample, with a mean age of 37.21±3.21 years. This is consistent with existing evidence highlighting that advanced maternal age is a critical factor influencing fertility outcomes. Fertility declines with age due to a reduction in both the quality and quantity of oocytes, making age a key determinant in the success of conception [23, 24]. These results underscore the importance of addressing fertility challenges early, particularly in older women seeking to conceive. Participants had a mean BMI of 23.12±2.94 kg/m², indicating that most were within a normal weight range. However, even slight deviations from an optimal BMI can have profound effects on reproductive health. Both obesity and underweight conditions are associated with hormonal imbalances that can impair ovulation, reduce conception rates, and lead to complications during pregnancy. Studies have shown that maintaining a healthy weight is vital for hormonal regulation and overall fertility [15]. It highlights the necessity of weight management as part of a comprehensive approach to addressing subfertility. The study's metabolic assessments revealed an average blood glucose level of 92.51±10.31 mg/dL and a mean HOMA-IR value of 2.31±0.82, indicating potential insulin resistance. Insulin resistance and hyperglycemia are closely linked to conditions such as polycystic ovary syndrome (PCOS) and type 2 diabetes, which are significant contributors to anovulation and infertility [23, 25]. Abnormal lipid profiles, including elevated cholesterol and triglyceride levels, further underscored the need for metabolic interventions. Dyslipidemia is a known risk factor for reproductive challenges and highlights the importance of lifestyle modifications to optimize metabolic and reproductive health [15]. Thyroid function assessments revealed that while 71.21% of participants were euthyroid, 24.08% had subclinical or overt hypothyroidism. Thyroid dysfunction, particularly hypothyroidism, disrupts the hypothalamic-pituitary-ovarian axis and is associated with reduced ovulation rates and poor pregnancy outcomes [26]. After three months of targeted intervention, significant improvements were observed in thyroid function. Mean TSH levels reduced from 7.42±2.09 mIU/L to 3.12±1.05 mIU/L, demonstrating effective management of hypothyroidism. This reduction is critical for restoring ovarian function and increasing fertility potential [25, 26]. Additionally, the normalization of Free T4 levels further reflected balanced thyroid hormone status, essential for ovarian health and implantation success [24]. Significant changes were observed in the biochemical profile of prolactin function among the study population over the three-month treatment period. Serum prolactin levels showed a notable reduction, declining from a baseline of 25.36 ± 5.24 ng/mL to 14.82 ± 4.09 ng/mL ($p< 0.001$). This decrease is particularly important, as elevated prolactin levels are well-documented to disrupt the hypothalamic-pituitary-ovarian (HPO) axis, contributing to anovulation and infertility. Alongside the decline in prolactin, significant reductions in LH and FSH levels were also recorded, highlighting a restoration of pituitary function. These findings are consistent with prior studies suggesting that hyperprolactinemia suppresses gonadotropin secretion, impairing ovarian activity and regular menstrual cycles [27]. Moreover, estradiol levels increased significantly, from 45.12 ± 12.38 pg/mL to 52.89 ± 13.27 pg/mL ($p< 0.05$), and progesterone levels rose markedly, from 1.21 ± 0.52 ng/mL to 5.62 ± 1.21 ng/mL ($p< 0.001$). The rise in estradiol indicates enhanced follicular development, likely attributed to the alleviation of prolactin's inhibitory effects on FSH and LH [28]. A notable improvement was seen in ovulation rates post-intervention, with 66.67% of participants achieving ovulation within three menstrual cycles. These results highlight the effectiveness of addressing metabolic dysfunction in improving reproductive outcomes. The findings are supported by previous studies, which show that optimizing metabolic parameters, such as glucose, insulin, lipids, and thyroid hormones, significantly enhances ovulatory function and increases pregnancy rates in women with subfertility [15, 23].

Limitations of the study

This study has several limitations. The use of purposive sampling may limit the generalizability of the findings to broader populations. The exclusion of patients with certain metabolic disorders or surgical histories might have introduced selection bias. The sample size, while adequate for preliminary insights, might not be large enough to detect fewer common effects or variations. The absence of long-term follow-up limits the understanding of sustained impacts of metabolic corrections on fertility outcomes beyond the study period.

Conclusion and Recommendation

This study highlights the significant impact of correcting metabolic factors on improving pregnancy rates in sub-fertile women. By addressing key parameters such as BMI, blood glucose, lipid profile, thyroid function, and serum prolactin, the interventions led to notable improvements in metabolic health and fertility outcomes. A majority of participants (66.67%) achieved ovulation within three cycles of treatment, and thyroid function metrics, including TSH and Free T4 levels, showed marked improvement over three months. These findings underscore the importance of comprehensive metabolic optimization in enhancing ovulatory function and increasing pregnancy success rates among sub fertile patients, particularly in the context of advanced maternal age and associated metabolic challenges.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee.

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