Original Article

Comparative Study on Different Hormones between Normal Pregnant Women and Women Experiencing Miscarriage

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Abstract

Background: Pregnancy leads to a complex alteration in hormonal levels and metabolism in the maternal and fetal system and if undesirable alteration is experienced, complications may be seen. Common complications of pregnancy include gestational diabetes, preeclampsia, preterm labor, and pregnancy loss or miscarriage. Miscarriage is defined as a spontaneous pregnancy loss occurring before 20 weeks of gestation. It has been seen in around 10%–15% of clinically recognized pregnancies. **Aim:** This study was designed to evaluate the levels of different serum hormones between cases and controls group. **Materials and Methods:** Pregnant women before 20 weeks of gestation were selected based on inclusion and exclusion criteria, visiting Adesh hospital Bathinda. After recording the history, blood was drawn and serum thyroid-stimulating hormones (TSH), total tri-iodothyronine (TT3), total thyroxine (TT4), prolactin and beta-human chorionic gonadotropin (β-hCG) were analyzed using TSOSH automated immunoassay analyzer. **Results:** Overall data and data of the 1st trimester suggested significant differences in the mean level of serum TT3, TSH, β-hCG, and prolactin between controls and cases ($P \leq 0.05$). However, serum TT4 did not show a significant difference ($P > 0.05$). In 2nd-trimester significant difference in the mean level of serum TSH was only observed between controls and cases ($P \leq 0.05$). Similarly, after applying Pearson's correlation, an inverse relation was only observed between serum TT3 and TSH of both control and cases ($P \leq 0.05$). **Conclusion:** This study emphasized that screening of women during pregnancy for different serum hormones may provide useful lead about the fate of pregnancy and better understanding of different hormones may reduce the rate of miscarriages and other complications related to pregnancy.

Keywords: *Gestation, hormones, miscarriage, pregnancy, trimester*

Introduction

Miscarriage is defined as a spontaneous pregnancy loss occurring before 20 weeks of gestation in the absence of elective medical or surgical measures to terminate the pregnancy.[1] It has been observed in 10%–15% of clinically recognized pregnancies and found 80% of miscarriages occur before 12 weeks of gestation, with miscarriage rates declining sharply after the first trimester.[2] The causes of pregnancy loss are reported to be multiple; anatomical variations, alterations in thrombosis, autoimmune, hereditary, infectious diseases, and endocrine diseases.[3] Although the vast majority of pregnant women have no preexisting endocrine abnormalities, a small percentage of women may develop endocrine alterations that could potentially lead to sporadic or recurrent miscarriage.[4] It is also estimated that approximately 8%–12% of all cases of recurrent pregnancy loss are caused by endocrine diseases.[5] Among different abnormalities, thyroid dysfunction is quite prevalent, and according to the World Health Organization, it became common among the general population affecting 750 million people worldwide and affects many organs, including the male and female gonads.[6,7] It was also found to interfere with human reproductive physiology, adversely influencing the outcome of the pregnancy and also in reducing the likelihood of pregnancy.[8] According to a study, thyroid hormones may also have an impact on the oocytes by affecting the granulosa and luteal cells and hence interfere with normal ovulation.[9] It is also well understood that low thyroxine levels have a positive feedback on thyroid-releasing hormone (TRH).[10] Also elevations in TRH have been associated

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with elevations in prolactin and it is believed that elevated prolactin alters the pulsatility of gonadotropin-releasing hormone and interferes with normal ovulation.[9] On the contrary, few studies suggest that the inadequate production of prolactin and its receptor in the endometrium during the implantation window cause premature luteolysis and recurrent miscarriages.[11] However, the underlying mechanisms and existing evidence are not constant throughout all species, and results from different studies are in disagreement. Therefore, this study was planned to identify the variation in different hormones related to pregnancy and were, thus, assessed as an attempt to identify the fate of pregnancy.

Materials and Methods

In this case-control study, 50 women were confirmed cases of spontaneous abortion/miscarriage and 50 were gestational age matching normal pregnant women (Visiting Gynaecology Department of Adesh Hospital, Bathinda). Considering 80% power of study, the sample size was calculated based on the finding of a previous study[12] by using online OpenEpi.com. Before enrolment, all the necessary details about this study were provided to the participants and informed written consent was obtained. The detailed history with the full clinical examination was recorded, and 3 ml of blood was drawn within 3 days of miscarriage and from gestational age-matched normal pregnant women under strict aseptic conditions. Serum thyroid-stimulating hormones (TSH), Total tri-iodothyronine (TT3), total thyroxine (TT4), prolactin, and beta-human chorionic gonadotropin (β-hCG) level were analyzed using TSOSH automated immunoassay analyzer at the central laboratory of Adesh Hospital Bathinda. All these works were started only after receiving the clearance from the Institutional Ethical Committee.

Inclusion criteria

Cases

Women with clinically confirmed cases of miscarriage.

Controls

Gestational age-matched pregnant women with no previously recognized miscarriage and no history of endocrine abnormality.

Exclusion criteria

Patients with a history of diabetes mellitus, polycystic ovary syndrome, heart disease, uterine fibroid, infectious disease, and non-consenting patients were excluded from this study.

Statistical analysis

Statistical analysis was performed using Microsoft excel. Karl Pearson's correlation was applied to the parameters of both controls and cases. Similarly, the mean values of different groups were also compared using Student's *t*-test to identify the statistically significant variations. Statistical analysis was performed between total data (i.e., 50 controls and 50 cases), 1st-trimester data (i.e., 30 controls and 30 cases) and between data of the 2nd trimester (20 controls and 20 cases). Statistically, significance difference was considered for all tests at ($P \leq 0.05$).

Results

This study was designed to verify the level of different hormones and to assess the association, if any, between different hormones of cases and controls. The results of the different groups are summarized.

It was observed that, mean ± standard deviation (SD) of serum TT3, TSH, β-hCG, and Prolactin were significantly different between controls and cases ($P = 0.009$), ($P = 0.001$), ($P = 0.007$), and ($P = 0.001$), respectively. However, mean ± SD of TT4 suggested no significant variation between controls (8.62 ± 0.94 μg/dl) and case (8.76 ± 1.04 μg/dl) ($P = 0.132$) [Table 1].

The difference of mean ± SD levels of serum TT3, TSH, β-hCG, and prolactin in the 1st trimester were also found to be statistically significant between controls and cases ($P = 0.049$), ($P = 0.001$), ($P = 0.047$), and ($P = 0.001$), respectively. However, the levels of TT4 in the 1st trimester do no suggest significant variation between controls (8.70 ± 0.77 μg/dl) and cases (8.82 ± 1.01 μg/dl) ($P = 0.592$) [Table 2].

While analyzing the various hormones in the 2nd trimester, it was found that difference in the mean TSH levels between controls and cases was highly significant ($P = 0.001$). However, TT3, TT4, β-hCG, and prolactin levels in the 2nd trimester suggest no statistically significant difference ($P > 0.05$) [Table 3].

A negative correlation between total data of control TT3 and TSH levels was suggested by Pearson's coefficient ($r = -0.28$) and ($P = 0.043$). However, the correlation between other parameters such as TT3 and TT4, TT4 and TSH, PRL and β-hCG of controls did not show any significant correlation ($P > 0.05$) [Table 4].

Similarly, after applying Pearson's correlation in cases, total data suggest a negative correlation between TT3 and TSH (r=-0.323) and ($P = 0.023$). However, the correlation between other parameters, TT3 and TT4, TT4 and TSH, PRL and β-hCG of cases did not show any significant correlation ($P > 0.05$) [Table 5].

This study suggested significant differences in the mean level of serum TT3, TSH, β-hCG, and prolactin between controls and cases. However, serum TT4 did not show a statistically significant difference ($P > 0.05$). Accordingly, data of the 1st trimester suggested similar variations, as mention above. However, in the 2nd trimester statistically significant difference in the mean level of serum TSH was

Table 1: Comparison of serum total tri-iodothyronine, total thyroxine, thyroid-stimulating hormones, beta-human chorionic gonadotropin and prolactin between total data of controls and cases using Student's *t*-test

Parameter	Mean±SD		Mean difference	*P*	Result
	Control (*n*=50)	Case (*n*=50)			
TT3 ng/dl	1.35±0.32	1.11±0.56	0.24	0.009	Highly significant
TT4 µg/dl	8.62±0.94	8.76±1.04	0.51	0.132	Not significant
TSH µIU/ml	2.54±1.0	5.74±3.42	3.19	0.001	Highly significant
β-hCG mIU/ml	42,520±13,504.1	35,620±11,519.9	6899.5	0.007	Highly significant
PRL ng/ml	48.52±14.11	37.07±11.08	10.84	0.001	Highly significant

TT3: Total tri-iodothyronine; TT4: Total thyroxine; TSH: Thyroid-stimulating hormone; β-hCG: Beta human chorionic gonadotropin; SD: Standard deviation; PRL: Prolactin

Table 2: Comparison of the 1st-trimester serum total tri-iodothyronine, total thyroxine, thyroid-stimulating hormones, beta-human chorionic gonadotropin, and prolactin between controls and cases using Student's *t*-test

Parameter of 1st trimester	Control (*n*=30)	Case (*n*=30)	Mean difference	*P*	Result
TT3 ng/dl	1.34±0.31	1.12±0.51	0.22	0.049	Significant
TT4 µg/dl	8.70±0.77	8.82±1.01	0.12	0.592	Not significant
TSH µIU/ml	2.43±0.99	5.38±3.19	2.94	0.001	Highly significant
β-hCG mIU/ml	41,398±12,196.9	35,914±10,397.3	5484.0	0.047	Significant
Prolactin ng/ml	49.43±13.0	36.87±10.32	12.55	0.001	Highly significant

TT3: Total tri-iodothyronine; TT4: Total thyroxine; TSH: Thyroid-stimulating hormone; β-hCG: Beta human chorionic gonadotropin; SD: Standard deviation; PRL: Prolactin

Table 3: Comparison of 2nd-trimester serum total tri-iodothyronine, total thyroxine, thyroid-stimulating hormones, beta-human chorionic gonadotropin, and prolactin between control and cases using Student's *t*-test

Parameter of 2nd trimester	Control (*n*=20)	Case (*n*=20)	Mean difference	*P*	Result
TT3 ng/dl	1.33±0.28	1.1±0.64	0.22	0.158	Not significant
TT4 µg/dl	8.52±1.17	8.66±1.11	0.14	0.692	Not significant
TSH µIU/ml	2.71±1.02	6.27±3.79	3.59	0.001	Highly significant
β-hCG mIU/ml	44,215±15,433.6	35,164±13,299.3	9050.0	0.054	Not significant
Prolactin ng/ml	47.16±15.88	38.87±12.32	8.28	0.073	Not significant

TT3: Total tri-iodothyronine; TT4: Total thyroxine; TSH: Thyroid-stimulating hormone; β-hCG: Beta human chorionic gonadotropin; SD: Standard deviation; PRL: Prolactin

Table 4: Pearson's correlation between the different hormones of control groups

Parameters (*n*=50)	*r*	*P*	Result
TT3 and TSH	−0.28	0.043	Significant inverse correlation
TT3 and TT4	0.089	0.54	Correlation was not significant at 0.05 level
TT4 and TSH	−0.17	0.215	Correlation was not significant at 0.05 level
PRL and β-hCG	0.277	0.052	Correlation was not significant at 0.05 level

TT3: Total tri-iodothyronine; TT4: Total thyroxine; TSH: Thyroid-stimulating hormone; β-hCG: Beta human chorionic gonadotropin; SD: Standard deviation; PRL: Prolactin

only observed and this might be the reason for the sharp decline in the rate of miscarriage in the 2nd trimester. Pearson's correlation suggested an inverse relationship between serum TT3 and TSH in both controls and cases. However, other parameters did not show any statistically significant correlations.

Discussion

Pregnancy is a physiological state accompanied by high-energy demand and an increased oxygen requirement, which leads to a complex alteration in metabolic and hormonal changes in the physiology of maternal and fetal system, and the requirement for thyroid hormones is increased during gestation.[13] Literature suggests that thyroid disorders may affect both the pregnant woman and the developing fetus. Development and maintenance of pregnancy are dependent on numerous endocrinological events that lead to the successful growth and development of the fetus and the fetus is completely dependent on the maternal thyroid hormones before 12 weeks of gestation.[14] Therefore, this study was carried out with a purpose to evaluate the levels of different serum hormones in women experiencing miscarriage as compared to gestational age-matched normal pregnant women.

The outcome of this study suggested a significant difference in the mean level of TT3, TSH, β-hCG, and prolactin between cases and controls. Similar results were

Table 5: Pearson's correlation between the different hormones in cases

Parameters (n=50)	r	P	Result
TT3 and TSH	−0.323	0.022	Significant inverse correlation
TT3 and TT_4	−0.012	0.934	Correlation was not significant at 0.05 level
TT4 and TSH	−0.018	0.901	Correlation was not significant at 0.05 level
PRL and β-hCG	0.045	0.204	Correlation was not significant at 0.05 level

TT3: Total tri-iodothyronine; TT4: Total thyroxine; TSH: Thyroid-stimulating hormone; β-hCG: Beta human chorionic gonadotropin

also seen in the 1st trimester of gestation between controls and cases. In the 2nd trimester, data suggested a significant variation only in the mean level of serum TSH. Other parameters such as TT3, TSH, β-hCG, and prolactin did not show any significant difference. Data of this study also suggested no significant variation in the mean level of TT4 between control and cases in any trimester ($P > 0.05$). Similar results were observed by Ramandeep *et al.,* 2017 suggesting universal screening for thyroid profile among pregnant women attending antenatal clinics and if alteration is observed, the proper suggestion should be taken from the treating doctor, and medication should be started to reduce thyroid manifestations in maternal complications.[12] A similar study also reported that women with TSH levels above 6 mIU/ml have a significantly increased risk for stillbirth and further risk of miscarriage increases by 15% for each 1 mIU/ml elevation of TSH level.[15,16] Similarly, the mean prolactin value of this study showed a statistically significant difference between control and cases. Consistent with the present study, one study revealed that lower basal serum prolactin concentration is associated with an increased risk of miscarriage in a subsequent pregnancy in women with unexplained recurrent miscarriage.[17] While few studies had also found hyperprolactinemia in the patients experiencing miscarriage.[18] Other findings of this study include a significant difference in the levels of β-hCG, and the mean level of β-hCG was high in controls as compared to cases. Similar to this result, Raman *et al*. 2016 also suggested women with low β-hCG levels are at a much higher risk of child loss. It also suggests hCG can stimulate the thyroid gland by binding with thyrotropin (TSH) receptor of the thyroid cell membrane during pregnancy due to its structural similarity to TSH, resulting in increased secretion of TT3 and partial suppression of serum TSH.[17] Therefore, this may be the pathophysiological mechanism for a slight increase in the level TT3 and low level of TSH in controls as compared to cases in this study. On the contrary, one study reported that there is no correlation between TSH and hCG levels.[19] However, 2nd-trimester findings of this study showed no significant differences in the mean level of β-hCG, and no significant variation in the level of different hormones were observed, which may be the explanation for the sharp decline in pregnancy loss during the 2nd trimester.

On the other hand, after applying Pearson's correlation, an inverse correlation between TT3 and TSH in total number of pregnancy and also in the 1st trimester of both controls and cases was found. Whereas, the correlation between TT3 and TT4, TT4 and TSH, Prolactin, and β-hCG did not show any significant relation between both the groups. Similarly, in the 2nd trimester, data of this study suggest no significant relationship between different hormones of controls and cases. This finding is similar to the results of Gahlawat *et al*., who reported a significant inverse relation between TT3 and TSH, indicating the existence of some feedback mechanism between the TSH and thyroid hormones. However, Gahlawat *et al*. also stated a significant inverse relation between TT4 and TSH, which is contradictory to the results of the present study.[20] Hence, the results of the study suggest marked variations in the levels of different hormones in 1st trimester of pregnancy, and therefore, better understanding the pathophysiology of these hormones can help in better outcomes of pregnancy.

The findings of this study are limited as variations were studied only for thyroid profile, prolactin, and β-hCG. Hence, further study on pregnancy-related hormones and identification of relationships between different hormones may help in better interpretation on the outcomes of pregnancy.

Conclusion

The findings of this study indicate that the screening of women for hormonal alteration may provide useful lead about the fate of pregnancy. It also suggests there was a significant variation in maternal serum hormones between normal pregnant women and women who experience miscarriage. Thus, it emphasized that a better understanding of different hormones may enable the clinicians to target the administration of potential therapies very early to women at high risk of miscarriage and thus, may prevent an unfavorable outcome.

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Conflicts of interest

There are no conflicts of interest.

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