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Original Research Article

Progesterone Supplementation in Women with Recurrent Pregnancy Loss

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Abstract:

Context: Recurrent pregnancy loss, the loss of three or more consecutive intrauterine pregnancies before 20 weeks of gestation with the same partner, affect 1%–1.5% of the pregnant population. The inadequate secretion of progesterone in early pregnancy has been proposed as a cause of recurrent pregnancy loss.

Aims: The aim was to investigate the role of progesterone supplementation in patients with recurrent pregnancy loss.

Settings and Design: This was a one year study from June 2021 to June 2022 of women with recurrent pregnancy loss who attended clinic at C.U. Shah Medical College & Hospital, Surendranagar at tertiary care center.

Subjects and Methods: 50 Women with at least two recurrent pregnancy losses were included in the study. For women with inadequate endogenous progesterone secretion, natural progesterone vaginal pessaries 200 mg 12-hourly were offered until 12 weeks gestation.

Results: Pregnancy cycles were analyzed to examine the pregnancy loss rate following progesterone supplementation. Majority of women from 21-25 age groups (48%).majority of women having 2 abortions (46%) and 14% women having hypothyroid. Overall live birth and pregnancy loss rates were 68% and 30%, respectively. When analyzed by the number of previous pregnancy loss there was a reduction in the pregnancy loss rate following progesterone supplementation in women with 3 previous pregnancy losses when compared with historical data.

Conclusions: Progesterone supplementation may have beneficial effects as progesterone needed for implantation and helps in women with luteal phase defect in unexplained recurrent pregnancy loss.

Keywords: Live Birth Rate, Pregnancy Loss Rate, Progesterone Vaginal Pessaries, Recurrent Pregnancy Loss.

Introduction

Recurrent pregnancy loss, the loss of three or more consecutive intrauterine pregnancies before 20 weeks of gestation with the same partner, affect 1%–1.5% of the pregnant population.[1] The pathophysiology of recurrent pregnancy loss is incompletely understood and despite investigation, no cause is found in more than 50% of cases.[2]. With a limited understanding of the aetiology, no specific treatment regimens can be offered, though several therapies with varying degrees of success have been proposed to prevent this condition.[3]

Progesterone maintains the early pregnancy and is mainly secreted by the corpus luteum during pregnancy.[5] Insufficient progesterone secretion and delayed endometrial development at the time of implantation or during early pregnancy may occur naturally or due to luteal phase defect and has been implicated as a cause of sporadic and recurrent pregnancy loss.[4] If progesterone supplementation reduces the risk of repeat pregnancy loss, the scientific basis for its use may be related in part to its role in the regulation of inflammatory mediators in pregnancy. Progesterone deficiency leads to increased levels of pro-inflammatory interleukin 8 (IL-8), cyclo-oxygenase-2, and monocyte chemoattractant protein-1 which destabilize the endometrium. Successful pregnancy is associated with the downregulation of pro-inflammatory T helper cell type 1 (Th-1) cytokines and upregulation of anti-inflammatory T helper cell type 2 (Th-2) cytokines. A 34-kDa protein, progesterone-induced blocking factor (PIBF) prevents inflammatory reactions by blocking Th-1 cytokines and natural killer cells degranulation and increasing asymmetric nontoxic blocking antibodies.[6]

Subjects and Methods

This was a prospective study of 50 women with recurrent pregnancy losses who attended our clinic over 1 years from June 2021 to June 2022 and who in the index pregnancy were noted to have subnormal early pregnancy progesterone secretion. Ethical approval was not required because there was no direct contact with the study population.

For all these women, prior to the index pregnancy, the following investigations were undertaken: follicle stimulating hormone (FSH), luteinizing hormone (LH), autoimmune antibodies, thyroid function tests, vaginal ultrasound scan, and, if indicated, hysterosalpingography or hysteroscopy to rule out uterine anomalies.

Women with two or more unexplained pregnancy losses were included. Early pregnancy surveillance was offered to all women with recurrent pregnancy losses in the form of initial and repeat (48 h later) serum progesterone. Women were advised to contact the clinic on the day of or the next day after the urinary pregnancy test was positive for progesterone measurement. A transvaginal ultrasound scan was performed at 6-weeks' gestation and again 2–3 weeks later when patients with on-going intrauterine pregnancies were referred to an antenatal clinic.

Table1: The outcome for women was analysed according to progesterone levels

Group	Initial Progesterone Value	Progesterone Value After 48 Hrs
1	<40nmol/L	No change
2	40nmol/L	Rise by less than 15%
3	40nmol/L	Rise by more than 15%

Progesterone supplementation was offered to all women in Groups I and II. Natural progesterone vaginal pessaries, 200 mg 12-hourly until the 12th week of pregnancy were offered. Group III with normal progesterone levels was not included in the analysis. The threshold for the diagnosis of progesterone insufficiency is based partly on published data showing levels of progesterone less than 40 nmol/L being associated with pregnancy loss, and on our own (unpublished) data (in ultimately successful pregnancies and a history of recurrent pregnancy loss, 95% of progesterone concentrations at all gestations from 5–12 weeks exceeded to 40 nmol/L).

A progesterone level of <20 nmol/L has a high positive predictive value for failing pregnancies. However, viable pregnancies have been reported with initial progesterone levels of <15.9 nmol/L (5 ng/mL).[7] Defining a discriminatory value using a single serum progesterone result is not helpful and at least two measurements are required. We chose the value of a 15% rise after 48 h based on our laboratory's data suggesting that a rise of 15% in the analyzed sample is required to be confident about the fact that a true rise in the progesterone level has actually occurred. Progesterone supplementation was started only in early pregnancy once suboptimal progesterone secretion was confirmed. Serum progesterone levels were not checked after progesterone supplementation because 200 mg twice daily natural progesterone vaginal pessaries have previously been shown to be adequate to maintain the serum progesterone levels to support the early pregnancy.[8] The end-point of the study was clinical pregnancy rate (by 10 weeks or more), calculating the number of women with ongoing pregnancy and pregnancy loss rate by calculating the proportions and 95% confidence intervals.

Results: According to the initial and 48-h repeat serum progesterone levels, there were total 50 patients. Overall, the median age of the women was 25 years (range 18–42) and the median number of pregnancy loss was 4 (range 3–9). This pregnancy cycles to be analyzed to examine the efficacy of progesterone supplementation. The live birth rate and repeat pregnancy loss rate after progesterone supplementation was 68% and 32% respectively.

Table 2: Progestogens Currently Available for the Treatment Of recurrent pregnancy loss

Generic Name	Trade Name	Unit Strength	Route Of Administration	Indicated For recurrent pregnancy loss
Hydroxyprogesterone caproate	Proluton Depot	250/500 mg/mL	Intramuscular injection	Yes
Dydrogesterone	Duphaston	10 mg	Oral tablet	Yes
Progesterone	Cyclogest	200/400 mg	Vaginal pessaries	No
Progesterone	Endometrin	100 mg	Vaginal tablet	No

Table 3: Age Distribution of the Study Group

Age Group In Years	Frequency	Percentage
18 - 20 yrs	4	8.0
21 - 25 yrs	24	48.0
26 - 30 yrs	18	36.0
31 - 35 yrs	2	4.0
Above 35 yrs	2	4.0
Total	50	100.0

Table 4: Obstetric Code of the StudyPopulation

Primary RPL	Secondary RPL
37	13

Obstetric Code	Frequency	Percentage
G3A2	23	46.0
G4A3	5	10.0
G4P1L0A2	3	6.0
G4P1L1A2	8	16.0
G5A4	3	6.0
G5P1L1A3	4	8.0
G6P1L1A4	3	6.0
G7A6	1	2.0
Total	50	100.0

Table 5: Hormonal Factors in the Study Group

Hormonal	Frequency	Percentage
Hashimotos	1	2.0
Hyperthyroid	3	6.0
Hypothyroid	7	14.0
No	39	78.0
Total	50	100.0

Table 6: pregnancy outcome

Outcome	Number of Women	Percentage
Live birth	34	68%
Subsequent pregnancy loss	16	32%

In the absence of a control group, we compared our data with similar historical data which showed subsequent pregnancy loss rates of 45% and 54% in women with previous three and four pregnancy loss, respectively.[9] In comparison with these data, our results demonstrated a reduction in the subsequent pregnancy loss rate in women with previous three pregnancy loss (35% vs. 45%) but the confidence limits overlapped (hence not likely to be statistically significant), while for women with previous four pregnancy loss, there was a further reduction in miscarriage rates (30% vs. 54%) with no confidence limit overlap.

Discussion

The study of treatments for recurrent pregnancy loss is fraught due to the desperation of the patients and the wide range of unaccredited treatments. This study has particular flaws, but reports on experience of practice in one unit with homogenous treatment policies managed by one individual. The RCTs published in the Cochrane database on recurrent pregnancy loss illustrate this difficulty; papers were published many years ago or had peculiar methodology (e.g., late recruitment – less than 10% receiving any intervention before 7 weeks gestation)[10,11]. The data we used as our comparative control are relatively unique in that they represent an unselected population cohort (approximately, 300,500 pregnancies) in the Danish population.[9]

The protective effect of previous live birth on the occurrence of repeat pregnancy loss in the future is not very clear and studies have shown different results.[12,13] We have not observed a protective effect of previous live birth on future pregnancy loss.

Progesterone has been used in different routes and doses to prevent miscarriage in early to mid-pregnancy. Although some early reports of progesterone use showed an improved outcome,[14] however, later studies showed conflicting results of beneficial effects of progesterone. El-Zibdeh showed that oral dydrogesterone reduced recurrent pregnancy loss

but the methodology in the paper is flawed due to the randomization and no proper concealment.[11]

Progesterone is an important pregnancy hormone and despite its longstanding use to treat recurrent pregnancy loss, insufficient data exist to support its widespread use. Most (90%) UK physicians remain unconvinced of any beneficial effects without a placebo-controlled randomized trial. Two randomized controlled trials of progesterone supplementation for recurrent pregnancy loss are awaited (20 mg oral dydrogesterone versus placebo for recurrent pregnancy loss; clinical trial number: NCT00193674; Cyclogest vaginal pessaries versus placebo, PROMISE study ISRCTN 92644181). These studies may provide clearer evidence for the role of progesterone in recurrent pregnancy loss management.

Conclusion

Considering that progesterone has important immunomodulatory functions by decreasing proinflammatory and increasing anti-inflammatory cytokines in early pregnancy, progesterone's role in maintaining early pregnancy is crucial. This study provides support that progesterone supplementation reduces the subsequent pregnancy loss rate in patients with unexplained recurrent pregnancy loss in comparison with historical data.

Although this study is limited by having no control group, the results contribute to the existing body of the literature on this subject which claims that progesterone supplementation may improve the pregnancy outcome in selected groups of unexplained recurrent pregnancy loss.

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