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Prednisone May Improve the Outcomes of Women with Recurrent Pregnancy Loss and Increased Levels of Peripheral Nk Cells: A Real World Clinical Report

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Abstract

Recurrent pregnancy loss is a major health problem that may involve nearly 3-5% of women in reproductive age. Several causes of recurrent pregnancy loss are well known and currently investigated and treated in daily practice. Immunological abnormalities are frequently discussed in this clinical setting although not clearly investigated, not only for diagnostics tools but also for a therapeutic support prompt to clinical outcome.

Increased levels of peripheral NK cells is in fact a well-recognized abnormality in women with unexplained recurrent pregnancy loss but studies on its treatment are lacking in the literature. We report a clinical series from our personal database on selected women with increased NK cells and recurrent pregnancy loss treated with low doses of prednisone.

Keywords: NK cells; Age; Infertility

Background

Recurrent pregnancy loss (RPL) represents a major health problem with two to three or more losses in up to 5% of women in reproductive age and it has been considered as one of the most common causes of female infertility [1].

Several reports identified many clinical conditions and diseases potentially responsible of RPL such as endocrine diseases (e.g. ovarian dysfunction, anovulation, hypopituitarism, diabetes), uterine malformations, genetic alterations (e.g. chromosomal aberrations), hypercoagulable state and thrombophilia (e.g. inherited thrombophilia, antiphospholipid syndrome, combined thrombophilia) [2-6]. Immunopathological chronic diseases have also been recognized as acquired causes of recurrent pregnancy loss, in particular systemic lupus erythematosus, while other immunological abnormalities as autoimmune and cellular abnormalities have also been considered as potential cause of RPL but less investigated in daily clinical practice. Increased percentage of peripheral NK lymphocytes has been associated to RPL in several reports in the literature but a clear percentage to be identified as risk factor in RPL is still lacking in daily clinical practice [7,8]. Our recent report identified a cut off of 10% of NK cells to split women with unexplained RPL and women without RPL [9]. The aim of this retrospective study is to investigate the role of treatment based on prednisone to improve the outcome of women with increased NK cells and RPL.

Patients and Methods

In order to understand if a therapeutic support with low doses of steroids may improve the outcome of women with unexplained RPL an NK cells peripheral percentage major than 10%, we selected 100 women referred to our outpatients clinic in the last two years for unexplained RPL and then we addressed them to low dose of prednisone (0.1-0.3 mg per-kg) in case of a new pregnancy.

In order to have a pure selected population of patients with recognized RPL due to chromosomal alterations, endocrine dysfunctions, chronic inflammatory diseases, infectious diseases, uterine malformations, tubal patency and thrombophilia, were excluded. For similar reasons, in order to escape clinical bias, patients that need to be treated during pregnancy with antibiotics or antithrombotics (i.e. aspirin or low molecular weight heparin) or steroids for any further reasons were also excluded from our analysis.

For this reason only 50 patients were eligible for this analysis.

The dose of prednisone was chosen according to the one described by Debono et al. [10] to start a similar treatment of any immunological chronic disease.

Results

Clinical characteristics and doses of prednisone used to treat selected patients were reported in Table 1. In our analysis we found that 45 patients treated with low doses of prednisone for increased NK peripheral levels in a new pregnancy, had delivery (after a personal history of RPL).

Levels of NK cells before and during prednisone treatment were reported in Table 2 for each patient.

Patient	Age	Smoker	Chromosomal abnormality	Uterine infection	Uterine malformation	Thrombophilia	Autoimmune disease	Antibiotics \steroids \antithrombotic for further reason	Prednisone doses (mg)	Outcome
1	32	No	No	No	No	No	No	No	No	D
2	34	No	No	No	No	No	No	No	No	M
3	31	No	No	No	No	No	No	No	No	D
4	29	No	No	No	No	No	No	No	No	D
5	39	No	No	No	No	No	No	No	No	D
6	42	No	No	No	No	No	No	No	No	D
7	44	No	No	No	No	No	No	No	No	D
8	38	No	No	No	No	No	No	No	No	D
9	37	No	No	No	No	No	No	No	No	D
10	36	No	No	No	No	No	No	No	No	D
11	25	No	No	No	No	No	No	No	No	D
12	41	No	No	No	No	No	No	No	No	D
13	42	No	No	No	No	No	No	No	No	D
14	33	No	No	No	No	No	No	No	No	D
15	34	No	No	No	No	No	No	No	No	PTD
16	34	No	No	No	No	No	No	No	No	D
17	31	No	No	No	No	No	No	No	No	M
18	35	No	No	No	No	No	No	No	No	D
19	40	No	No	No	No	No	No	No	No	D
20	36	No	No	No	No	No	No	No	No	D
21	32	No	No	No	No	No	No	No	No	D
22	32	No	No	No	No	No	No	No	No	D
23	38	No	No	No	No	No	No	No	No	D
24	36	No	No	No	No	No	No	No	No	D
25	35	No	No	No	No	No	No	No	No	D
26	41	No	No	No	No	No	No	No	No	M
27	40	No	No	No	No	No	No	No	No	D
28	37	No	No	No	No	No	No	No	No	D
29	34	No	No	No	No	No	No	No	No	D
30	36	No	No	No	No	No	No	No	No	D
31	39	No	No	No	No	No	No	No	No	D
32	49	No	No	No	No	No	No	No	No	PTD
33	40	No	No	No	No	No	No	No	No	D

34	31	No	No	No	No	No	No	No	No	D
35	30	No	No	No	No	No	No	No	No	D
36	34	No	No	No	No	No	No	No	No	D
37	32	No	No	No	No	No	No	No	No	PTD
38	35	No	No	No	No	No	No	No	No	D
39	40	No	No	No	No	No	No	No	No	D
40	32	No	No	No	No	No	No	No	No	M
41	35	No	No	No	No	No	No	No	No	D
42	37	No	No	No	No	No	No	No	No	D
43	39	No	No	No	No	No	No	No	No	D
44	37	No	No	No	No	No	No	No	No	D
45	40	No	No	No	No	No	No	No	No	M
46	33	No	No	No	No	No	No	No	No	D
47	29	No	No	No	No	No	No	No	No	D
48	36	No	No	No	No	No	No	No	No	D
49	30	No	No	No	No	No	No	No	No	D
50	32	No	No	No	No	No	No	No	No	D
D: delivery; M: miscarriage; PTD: pre term delivery										

Table 1: Clinical characteristics of patients with RPL and increased NK cells treated with low doses of prednisone.

Further complications as intra uterine growth restriction (IUGR) or pre term delivery (PTD) were also observed.

Only 5 patients showed a new miscarriage, 45 patients showed delivery, 30 with natural delivery and 15 after caesarean section; IUGR were not recorded in any case of delivery, while PTD were detected in 3 cases.

Patient	Age	NK cells before prednisone (%)	NK cells during prednisone
1	32	18	7
2	34	15	10
3	31	21	9
4	29	18	8
5	39	29	10
6	42	19	8
7	44	12	6
8	38	11	5
9	37	13	8
10	36	18	7
11	25	16	6
12	41	16	7
13	42	12	8
14	33	21	8
15	34	21	7
16	34	19	5
17	31	26	14
18	35	15	7
19	40	14	8
20	36	20	9
21	32	19	6
22	32	16	7
23	38	17	6
24	36	20	10
25	35	18	8
26	41	16	14
27	40	19	10
28	37	13	8

29	34	16	9
30	36	12	5
31	39	21	6
32	49	26	7
33	40	32	7
34	31	18	8
35	30	12	6
36	34	15	8
37	32	21	8
38	35	18	7
39	40	28	8
40	32	24	13
41	35	16	8
42	37	19	7
43	39	21	7
44	37	15	6
45	40	18	9
46	33	16	7
47	29	23	8
48	36	14	7
49	30	16	6
50	32	18	9

Table 2: Levels of NK cells in women with RPL before and during treatment with prednisone.

Discussion

In several reports in the literature, impaired immunological functions have been described in most of pregnant women because also of the identification by immune system of paternal antigens present in the fetus; several authors postulate this as a key point of mechanisms involved in the following RPL [11]. From a pathophysiological point of view several immune functions as migration of immune cells, cytokine production and impaired lymphocytes T ratio have been most frequently underlined in these clinical conditions, in the literature. Immune cells most frequently associated to migration to uterine district are peripheral blood monocytes (PBMc) and Natural Killer cells (NKc), and the responsible cytokines are mainly produced by PBMc and lymphocytes T helper. Endocrine and paracrine productions of female sexual hormones seem to be also associated to the increase of NKc in the decidual endometrium during the implantation [12] giving so further attention to the balance between peripheral NKc *vs.* uterine NKc as potential responsible of abnormal immune response toward fetus [12,13]. From a clinical point of view increased levels of NK cells have been found in selected populations of patients with RPL vs healthy subjects and *vs.* patients with end stage kidney failure [14,15]. A similar correlation has also been found in patients with miscarriages after a successful pregnancy obtained after an in vitro fertilization procedure [16].

On the other side little is known from a therapeutic point of view, in this clinical setting. In clinical practice any type of excess of lymphocyte-count benefits of a treatment with steroids. NK cells are better defined as natural killer lymphocyte, so our clinical attempt was to verify if a treatment with low doses of prednisone could be useful in clinical practice to reduce the activity and the number of peripheral NK cells. Yet, although the reduction of levels of NKc seem to be possible with the use of steroids, no one reported an appropriated dose of steroids that can be used in this clinical setting in specific studies, so we tried to find an appropriate dose starting with a low dose treatment.

Results were positive from a clinical point of view because the outcome of pregnancy was positive in 90% of patients, although several considerations should be performed as a study limitation.

First of all our report is a report of clinical practice and not a trial, so our results should be confirmed on large population; the second relevant aspect is related to the fact that our population was selected and screened for any other cause of RPL; finally, being a selected population not treated with further drugs, these results should be confirmed in patients with increased clinical complexity (i.e. other clinical conditions associated to RPL).

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