Maternal and Neonatal Complications in Pregnant Women with Mitral Stenosis

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ABSTRACT: **Background:** Rheumatic mitral stenosis (MS) is a relatively rare diagnosis in the developed countries. Its treatment during pregnancy is challenging due to hemodynamic changes. With the demographic changes due to recent waves of immigration, an increase in the prevalence of rheumatic heart disease is expected.

Objective: To evaluate maternal and neonatal complications in patients with mitral stenosis.

Methods: During the years 2006–2017, 22 women who underwent 31 pregnancies were followed at the Sheba Medical Center in Israel. We collected data regarding hemodynamic changes and their clinical course. MS was classified as mild, moderate, or severe according to mitral valve area by echocardiography. Maternal and fetal adverse events were evaluated according to severity of MS and compared by Poisson regression modeling.

Results: MS was severe in 7 pregnancies (22.6%), moderate in 9 (29%), and mild in 15 (48.4%). Twenty patients were managed conservatively and 2 underwent a successful percutaneous mitral balloon valvuloplasty (PBMVP) during pregnancy. All pregnancies ended with a liveborn neonate and no maternal mortality. Peak and mean mitral pressure gradients increased during pregnancy from 13.3 ± 5.3 to 18.6 ± 5.1 mmHg and from 5.9 ± 2.3 to 9.6 ± 3.4 mmHg respectively ($P < 0.05$). Eight pregnancies (25.8%) were complicated by pulmonary congestion, 2/15 (13.3%) with mild MS, 2/9 (22.2%) with moderate, and 4/7 (57.1%) with severe MS. The adverse event rate was higher among patients with severe MS compared with moderate and mild MS [hazard ratio (HR) 3.15, 95% confidence interval (95%CI) 1.04–9.52 and HR 4.06, 95%CI 1.4–11.19 respectively, $P < 0.05$]. Nine of 31 deliveries were vaginal; 6 of 22 cesarean sections (27.3%) were performed for cardiac indications.

Conclusions: The number of total adverse events was higher among patients with severe MS. Patients with moderate and mild MS should be treated attentively, but good obstetric and maternal outcome can be expected.

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KEY WORDS: maternal complications, mitral stenosis (MS), pregnancy outcome, rheumatic heart disease, echocardiography

Healthy women experience extensive hemodynamic changes during pregnancy. Both blood volume and heart rate increase, and there is a decline in peripheral resistance and blood pressure. Mitral stenosis (MS) is the most common valvular disease in pregnancy. Pressure gradients over the stenotic mitral valve are strongly related to heart rate and circulating volume, so that pregnancy commonly leads to an aggravation of cardiac symptoms in these women [1,2].

Studies on the outcome of pregnant patients with mitral stenosis have been published from several countries, including Canada, the United States and Brazil [3-5]. In Israel, only one large series of patients with rheumatic heart disease (RHD) has been described. That series, which included also patients with mitral stenosis, was reported almost 40 years ago. It was a retrospective analysis of patients diagnosed with RHD during the years 1945–1948 and their follow-up 30 years later [6].

In the past decade there has been a decrease in prevalence of rheumatic heart disease in developed countries, although it is highly prevalent in some parts of Asia and Africa [7]. Due to recent immigration waves from developing countries to Europe, the rate of RHD is expected to increase in that region. In the current literature only a few hundred deliveries and their outcomes have been described [1,8-10].

The purpose of the present study was to evaluate the updated clinical course, and the maternal and fetal outcomes of pregnant women with mitral stenosis referred to our tertiary care center for the treatment of pregnant women with cardiac disease.

PATIENTS AND METHODS

All pregnant women with mitral stenosis who were referred to our specialized Pregnancy with Heart Disease clinic at Sheba Medical Center during the years 2006–2017 were included in this retrospective cohort study. All 22 patients were followed during their 31 pregnancies by our multidisciplinary Cardiology-Maternal-Fetal-Medicine team. Stable patients were evaluated once every 2 months until the end of the second trimester, once a month during the next 2 months, and once every 2 weeks during the last month of pregnancy. Symptomatic patients were followed every 1 or 2 weeks according to their clinical status. Echocardiography was performed once per tri-

mester or when clinically indicated. General and obstetric history, demographic information, clinical and echocardiographic data, and neonatal data were obtained during various clinic visits and hospitalizations up until the postpartum period. Collected data included the following: maternal age, gestational age at enrollment, previous obstetric history, co-morbidities before pregnancy, associated cardiac disease, previous percutaneous mitral balloon valvuloplasty (PBMVP), previous cardiac surgeries, and any other severe chronic illnesses. Echocardiographic data before, during, and immediately after pregnancy were collected. All echocardiography data were reviewed and validated by a specialized echocardiographist (R.K.). Echocardiographic data were evaluated according to the current guidelines, and included mitral valve area, and peak and mean gradient across the stenotic valve. Associated mitral, aortic and tricuspid regurgitation were also evaluated and classified as mild, moderate or severe according to guidelines [11,12]. Estimated pulmonary arterial pressure was measured according to the tricuspid regurgitation pressure gradient and evaluation of the inferior vena cava. Ejection fraction (EF) was visually estimated.

Patients with a mitral valve area < 1 cm^2 were classified as having severe MS, 1.0–1.5 cm^2 as moderate MS, and 1.5–2 cm^2 as mild mitral stenosis. We also retrieved data on the etiology, New York Heart Association (NYHA) Functional Classification, previous or present arrhythmia, and medical treatment at the beginning of pregnancy and after birth.

Maternal complications were defined as pulmonary edema and congestion during pregnancy, arrhythmias, stroke, need for cardiac interventions, pulmonary emboli, chorioamnionitis, and maternal death.

Fetal complications were defined as premature delivery, small-for-gestational age (birth weight less than the 10th percentile for gestational age), and fetal or neonatal death. Obstetric data included gestational age at delivery, mode of delivery, indication for delivery, birth weight, and birth weight percentile according to standards in the liveborn population in Israel [13].

This study was approved by the institutional review board.

STATISTICAL ANALYSIS

Continuous variables were compared using Student's *t*-test, and categorical data were compared using the χ^2 test. For comparing adverse outcomes, we used the Poisson regression model. The statistical model was adjusted according to total gestational weeks. All results were considered statistically significant for a two-sided *P* value < 0.05. All analyses were two-tailed and performed with the SPSS version 22 statistical software (IBM Inc., Chicago, IL, USA).

RESULTS

From 2006 to 2017, 22 women with mitral stenosis were followed in our clinic (31 pregnancies). Baseline characteristics of these pregnancies are displayed in Table 1. The mean maternal age was 30.97 ± 5.59 years. Seven pregnancies (22.6%) started with severe mitral stenosis, 9 (29.03%) with moderate MS, and 15 (48.4%) with mild MS. Twenty-one pregnancies started in NYHA functional class I or II. Four patients with previously unknown disease presented with pulmonary edema during pregnancy (one of them presented with acute pulmonary edema during delivery). All four patients stabilized clinically with medical therapy. Two patients underwent PBMVP during pregnancy. One was a patient with previously unknown disease who presented with severe mitral stenosis, mild aortic stenosis and moderate aortic regurgitation. As a result of her clinical deterioration she was referred to our care; however, she was unresponsive to medical treatment and underwent a successful valvuloplasty in the 20th week of pregnancy. She stabilized clinically and was delivered by cesarean section at 39 weeks gestation for obstetric indications. The second patient was an immigrant from Sri Lanka, also without a previous diagnosis, who deteriorated clinically to NYHA functional class III and first presented with a pulmonary artery pressure of 80 mmHg. She underwent PBMVP in the 33th week of gestation and had a normal vaginal delivery at 37 + 6 weeks without any complications.

PBMVP was performed in another five patients in association with pregnancies. Patient #7 underwent the first PBMVP after her first delivery, stabilized clinically, and gave birth later three more times [Table 1]. After the first procedure she had mild mitral regurgitation (MR), which aggravated to moderate MR during a subsequent pregnancy. Between the third and fourth pregnancies she deteriorated clinically, had a second valvuloplasty, and developed severe mitral regurgitation without clinical deterioration. She became pregnant against medical advice, and her pregnancy was without complications. An additional four patients underwent preventive PBMVP after pregnancy. One of them (who had her second PBMVP) developed severe MR and clinically deteriorated to NYHA functional class III, but became pregnant twice again contrary to medical advice. She completed both pregnancies without further clinical deterioration and without major complications.

In our cohort, the mean gestational age at delivery was 37.12 ± 3.39 weeks. Nine of 31 deliveries were vaginal (29.0%). Six of 22 cesarean sections (27.3%) were performed for cardiac indications. Two patients underwent cesarean section due to pulmonary edema. The first was a patient with previously unknown severe mitral stenosis who arrived at the hospital undiagnosed in acute pulmonary edema which developed during delivery. The second was a patient with mild mitral stenosis who was not under our care, did not report about her condition, and developed pulmonary edema after receiving intravenous fluids upon arrival at the Ob-Gyn emergency department just prior to delivery. Other indications for cesarean section were progressive and aggravating dyspnea unresponsive to optimal medical therapy, and a combination of intrauterine growth retardation

Table 1. Baseline characteristics of mitral stenosis patients at the beginning of pregnancy

Patient no.	Maternal age (yrs)	Interventional procedures before pregnancy	Mitral stenosis degree	Associated valve disease	Mitral stenosis etiology	NYHA functional class	Estimated pulmonary pressure (mmHg)	Medical treatment
1	32	PBMVP X 2 s/p mitral comissurotomy	Mild	No	Rheumatic	I	39	Yes
2	37	PBMVP X 2	Mild	Severe AS	Rheumatic	I	21	Yes
3	36	PBMVP X 1	Mild	No	Rheumatic	II	38	Yes
4	32	s/p VSD repair	Mild	No	Congenital	II	35	No
5	33	s/p MVP repair	Mild	Moderate MR	Marfan	I	25	No
6	45	No	Moderate	Moderate MR	Rheumatic	I	31	Yes
7P1	25	No	Severe	Severe TR	Rheumatic	I	Not available	No
7P2	27	PBMVP X 1	Moderate	Moderate TR	Rheumatic	I	28	Yes
7P3	30	PBMVP X 1	Severe	Moderate TR	Rheumatic	II	48	Yes
7P4	31	PBMVP X 2	Mild	Moderate MR + TR	Rheumatic	II	40	Yes
8	27	No	Severe	Mild AS Moderate AR	Rheumatic	III	Not available	No
9P1	21	PBMVP X 2	Moderate	No	Rheumatic	I	Not available	Yes
9P2	22	PBMVP X 3	Moderate	Severe MR	Rheumatic	I	45	Yes
9P3	27	PBMVP X 3	Moderate	Severe MR	Rheumatic	III	31	Yes
10	35	No	Moderate	Moderate AS + AR	Rheumatic	I	27	Yes
11	31	PBMVP X 1	Mild	Severe MR	Rheumatic	I	21	No
12	29	No	Mild	Severe MR Moderate TR	Rheumatic	I	Not available	No
13	27	No	Severe	Moderate TR	Rheumatic	I	Not available	Yes
14P1	24	No	Mild	Moderate AR	Rheumatic	I	Not available	Yes
14P2	28	PBMVP X 1	Mild	Severe AR	Rheumatic	III	28	Yes
15P1	37	PBMVP X 1	Moderate	No	Rheumatic	I	Not available	Yes
15P2	41	PBMVP X 1	Moderate	No	Rheumatic	I	35	No
16	38	No	Moderate	No	Rheumatic	I	35	No
17	37	s/p coarctation	Mild	No	Congenital	I	Not available	No
18P1	30	No	Severe	Moderate AR	Rheumatic	I	Not available	No
18P2	34	PBMVP X 1	Severe	No	Rheumatic	II	30	No
19P1	28	No	Severe	No	Rheumatic	I	Not available	No
19P2	31	PBMVP X 1	Mild	No	Rheumatic	I	26	No
20	24	No	Mild	No	Rheumatic	I	25	No
21	34	PBMVP X 1	Mild	No	Rheumatic	I	Not available	No
22	27	s/p mitral comissurotomy and repair	Mild	Moderate MR+TR	Rheumatic	I	35	No

NYHA = New York Heart Association Functional Classification, PBMVP = percutaneous mitral balloon valvuloplasty, COPD = chronic obstructive pulmonary disease, FMF = familial Mediterranean fever, CVA = cerebrovascular accident, AS = aortic stenosis, MR = mitral regurgitation, AR = aortic regurgitation, TR = tricuspid regurgitation

(IUGR) and severe symptoms. The remaining cesarean sections were obstetrically indicated (previous cesarean section, lack of progression, breech position, and placenta acreta).

One patient (#6, Table 1) with moderate MS had delivered at the 25th week of gestation. Her medical background included chronic obstructive pulmonary disease (COPD) and familial Mediterranean fever (FMF). She was not under follow-up and was hospitalized during the 18th week with pneumonia and eventually diagnosed with pulmonary edema. In the 25th week of gestation she had a high fever and was diagnosed with chorioamnionitis. An emergency cesarean section was conducted and she gave birth to a 900 g boy. The newborn and his mother were later discharged from hospital without any complications. The maternal and fetal complications during pregnancy according to severity of mitral stenosis are listed in Table 2.

Eight pregnancies (25.8%) were complicated by pulmonary congestion, 2 of 15 (13.3%) had mild MS, 2/9 (22.2%) had moderate, and 4/7 (57.1%) had severe MS. Patients with severe MS had much higher rates of pulmonary edema than those with moderate MS ($P = 0.05$). Other maternal complications

included cerebrovascular accident (one pregnancy), pulmonary emboli (one pregnancy), and chorioamnionitis (one pregnancy) as previously mentioned [Table 2]. All pregnancies terminated with a liveborn child, 5 (16.6%) were preterm deliveries before the 37th week of gestation, and 6 children (19.3%) were born small-for-gestational weight according to standards in the liveborn Israeli population [13]. The total adverse-event rates were higher among patients with severe MS when compared to moderate and mild MS [hazard ratio (HR) 3.15, 95 confidence interval (95%CI) 1.04–9.52, and HR 4.06, CI 1.4–11.19 respectively; $P < 0.05$ for all).

All patients had a normal ejection fraction. Most pregnancies (n = 28, 90.3%) started in functional class I and II, and during 20 pregnancies (64.5%) there was a deterioration of at least one functional class [Figure 1]. Peak mitral pressure gradient rose from 13.3 ± 5.3 to 18.6 ± 5.1 and mean gradient from 5.9 ± 2.3 to 9.6 ± 3.4 respectively ($P < 0.05$ for all). The changes in peak and mean mitral pressure gradients are illustrated in Figures 2A and 2B. The estimated pulmonary artery pressure rose from 32.3 ± 7.7 to 40.28 ± 9.55 mmHg ($P < 0.05$). These changes were reflected by an increased need for medical treatment during pregnancy. While 17 pregnancies started without any medical treatment, only 2 finished without treatment with beta-blockers or diuretics ($P < 0.05$). The mean hemoglobin level before delivery was 11.36 mg/dl in this cohort of patients. Three patients received blood transfusions and two received iron transfusions during pregnancy. None of our patients presented with cardiac arrhythmia during pregnancy.

Table 2. Maternal and fetal complications according to mitral stenosis degree

Complication	Mitral stenosis degree		
	Mild N=15	Moderate N=9	Severe N=7
Maternal complications			
Pulmonary edema and congestion (%)	2 (13.3)	2 (22.2)	4 (57.1)
PBMVP during pregnancy (%)	0	0	2 (28.6)
Cerebrovascular accident (%)	0	1 (11.1)	0
Pulmonary emboli (%)	1 (6.7)	0	0
Amnionitis (%)	0	1 (11.1)	0
Fetal complications			
Small for gestational age* (%)	2 (13.3)	1 (11.1)	3 (42.3)
Preterm delivery (%)**	2 (13.3)	1 (11.1)	1 (14.2)

*Small for gestational weight defined as birth weight ≤ 10th percentile according to birth weight standards in the liveborn population in Israel.

**Preterm delivery defined as delivery before 37 weeks of gestation.

PBMVP = percutaneous mitral balloon valvuloplasty

Figure 1. NYHA Functional Class change during pregnancy in patients with mitral stenosis

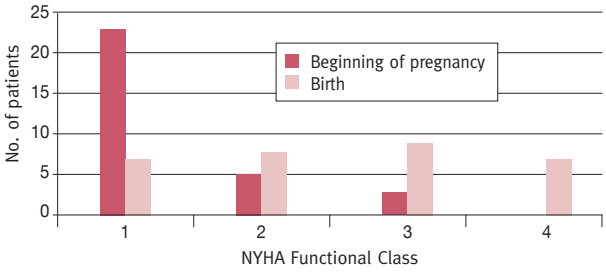
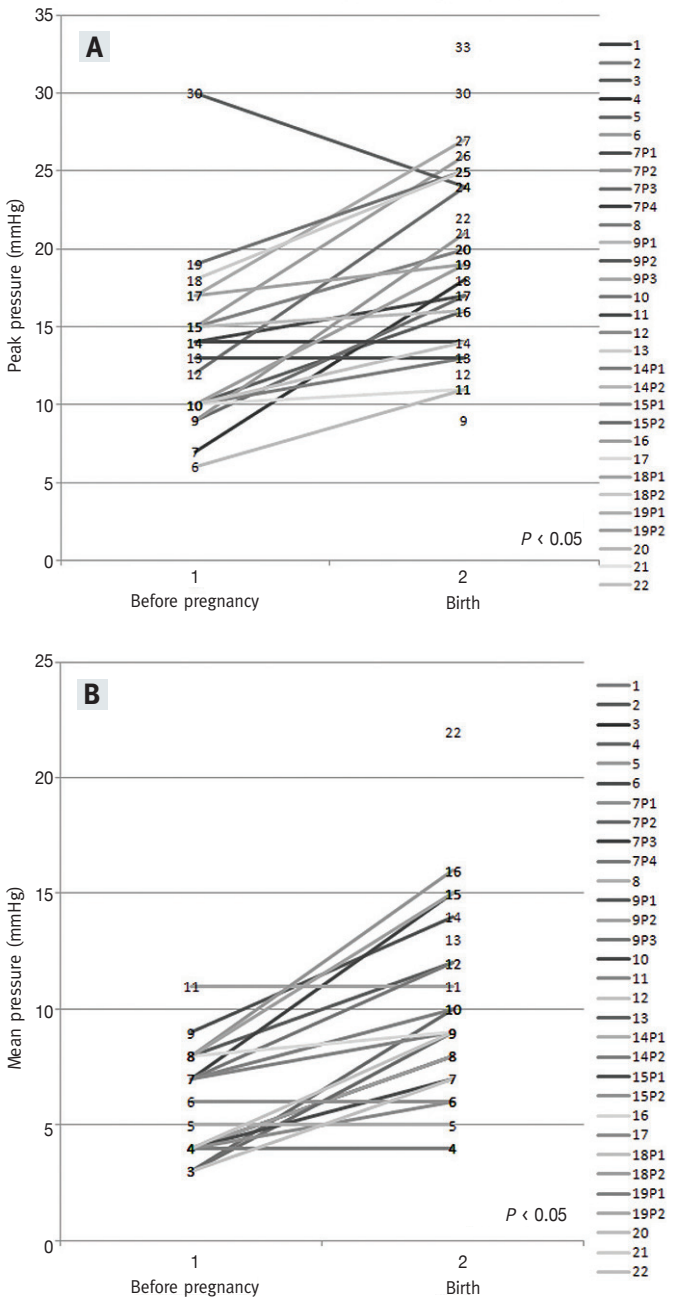


Figure 2. [A] Peak pressure change during pregnancy. **[B]** Mean pressure change during pregnancy



DISCUSSION

Managing mitral stenosis during pregnancy remains a clinical challenge, and some findings were striking in this series. First, like previous studies, we have shown that the increased pressure gradients over the stenotic mitral valve during pregnancy are reflected by the aggravation of symptoms and the need for an increase in medical therapy, and sometimes by the need for intervention [14,15]. Second, even with modern care and an efficient healthcare system (in Israel almost all adolescents are examined at school and before military service), there are patients who reach childbearing age undiagnosed and manifest their disease for the first time during pregnancy. Third, the hemodynamic changes of pregnancy may lead to an important clinical deterioration regardless of the severity of the baseline mitral stenosis. Fourth, despite the clinical deterioration and increased morbidity, with continuous and meticulous follow-up, there was no maternal or fetal mortality.

Hemodynamic changes during pregnancy can unmask undiagnosed rheumatic heart disease or decompensate already known heart disease, as was shown in our series of patients. Even though rheumatic heart disease rates have declined in developed countries, it is still a major risk factor for maternal and fetal morbidity and mortality. Major series of pregnant patients with mitral stenosis described by Hameed et al. [3] and Silversides at al. [4] had characteristics similar to our case series. Cardiac morbidity in these studies was around 30%. Interestingly, and in contrast to these previous studies, no major cardiac arrhythmias were detected in our series. Even the patient who was admitted after a minor cerebrovascular accident was extensively investigated and found to be in normal sinus rhythm. Also, similar to our findings, adverse maternal and fetal outcome were strongly associated with mitral stenosis severity, and almost all the patients were successfully managed medically [1,2]. In contrast to their excessive maternal and cardiac morbidity, these pregnancies were not associated with mortality. The common mortality rate associated with pregnancy in the literature is less than 1% [1-5].

The major therapeutic challenge in managing pregnancy in patients with severe MS is decompensated heart failure that does not respond to medical treatment. In these patients PBMVP may be performed during pregnancy, usually by the end of the second or the beginning of the third trimester. There are several case reports and a large study by Vinayakumar and co-workers who reported successful rates of PBMVP during pregnancy with clinical and hemodynamic improvement [16-20]. In our series there were two cases of a successful PBMVP during the second and third trimesters of pregnancy. For this purpose and in order to avoid the clinical deterioration during pregnancy, both the American and the European guidelines [21,22] advocate the use of BMVP before pregnancy in patients with an MVA < 1.5 cm^2 irrespective of symptoms. That was the case for four of our patients in whom PBMVP was performed before allowing new pregnancies.

In this series, as well as in previous ones [3,4], fetal adverse outcomes were highly prevalent, the prevalence increasing with the severity of disease. We found a much higher rate of preterm deliveries and low birth weight than in the general population. In our study 16.6% of deliveries were preterm and 19.3% were born small for their gestational age. Surprisingly, we had a higher rate of preterm delivery among patients with moderate MS than among those with severe disease, but the numbers are small. This difference contrasts with the findings of Silversides et al. [3] and is probably due to rigorous medical treatment in patients with severe disease and the use of PBMVP in patients unresponsive to medical treatment. Importantly, it is still uncertain whether PBMVP during pregnancy can affect fetal outcome [23,24].

The cesarean section rate was 69% among our patients, higher than in the general Israeli population (17.7%). Although the cesarean section rate was relatively high in our cohort (69%), only 27.3% were due to cardiac indications and the rest to various obstetric factors. This is in accordance with a 20% cesarean section rate for cardiac indications in the published literature [1,3]. Most cesarean sections were performed due to fetal indications or repeat cesarean surgery; the preferred delivery mode in this population is still vaginal [2,4].

LIMITATIONS

Several pregnancies were associated with other valvular disorders. This is an important confounder that may influence clinical symptoms and complications.

This was a small-scale study in a single tertiary medical center. Four patients were first diagnosed with mitral stenosis after severe clinical deterioration during pregnancy. Had they been identified and diagnosed previously, starting pregnancy under specialized cardiac care would have assured a better maternal and fetal outcome.

CONCLUSIONS

Managing pregnant patients with mitral stenosis continues to be a challenge, and data regarding maternal and fetal outcome are limited. Severe mitral stenosis is a major risk factor for adverse outcomes such as cardiac pulmonary congestion and fetal small-for-gestational age. Pregnant patients with MS require meticulous care, and PBMVP should be considered before pregnancy and sometimes even during pregnancy.

With the expected increase in the prevalence of rheumatic heart disease in the developed world due to recent demographic changes, a renewed interest in this area is warranted and data regarding contemporary care of these patients are needed.

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Capsule

Regulatory T cells mediate specific suppression by depleting peptide-MHC class II from dendritic cells

Regulatory T cells (Treg cells) can activate multiple suppressive mechanisms in vitro after activation via the T cell antigen receptor, resulting in antigen-independent suppression. However, it remains unclear whether similar pathways operate in vivo. **Akkaya** et al. found that antigen-specific Treg cells activated by dendritic cells (DCs) pulsed with two antigens suppressed conventional naive T cells (Tnaive cells) specific for both cognate antigens and non-cognate antigens in vitro but suppressed only Tnaive cells specific for cognate antigen in vivo. Antigen-specific Treg cells formed strong interactions with DCs, resulting in selective inhibition of the binding of Tnaive cells to cognate antigen, yet allowed bystander Tnaive cell access. Strong binding resulted in the removal of the complex of cognate peptide and major histocompatibility complex class II (pMHCII) from the DC surface, reducing the capacity of DCs to present antigen. The enhanced binding of Treg cells to DCs, coupled with their capacity to deplete pMHCII, represents a novel pathway for Treg cell-mediated suppression and may be a mechanism by which Treg cells maintain immune homeostasis.

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Eitan Israeli

"Failure will never overtake me if my determination to succeed is strong enough"

Og Mandino (1923–1996), American author, whose bestselling book *The Greatest Salesman in the World* sold over 50 million copies and was translated into over twenty-five different languages. He was the president of *Success Unlimited* magazine until 1976 and is an inductee of the National Speakers Association's Hall of Fame