The Impact of Type, Dosage and Time of Prenatal Steroid Administration on Neonatal Outcome

Zareba-Szczudlik J., Dobrowska-Redo A, Malinowska-Polubic A and Romejko-Wolniewicz E

Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland

Corresponding author: Julia Zareba-Szczudlik, MD, PhD, Department of Obstetrics & Gynecology, Medical University of Warsaw, Karowa Street 2, 00-315 Warsaw, Poland, Tel: +48 607681717, Fax: +48 22 5966487, E-mail: juliaszmed@wp.pl

Received date: Feb 23, 2016; Accepted date: Apr 25, 2016; Published date: Apr 30, 2016

Copyright: © 2016 Zareba-Szczudlik J, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: In 1972, Liggins and Howie demonstrated that antenatal steroid administration reduced the incidence of respiratory distress syndrome and perinatal mortality in neonates. Since the publication of these findings, perinatal and long-term results of steroid therapy have been evaluated in numerous studies. The aim of the review was to compare the impact of type, dosage, and time of prenatal steroid administration on perinatal outcomes in neonates and in mothers.

Summary: Although the results of the studies are ambiguous, one should consider the potential benefits of dexamethasone in cases of risk of preterm delivery due to abnormalities in fetal heart assessments. Dexamethasone may also lead to better results when preterm neonates are burdened with cardiovascular defects or diseases. The opposite holds true for abnormal flows within UA or fetal MCA, i.e., one should consider whether betamethasone is the appropriate drug of choice. Steroid treatment after 34 weeks of gestation is not beneficial. Administration of the full course of steroid treatment (24 mg) in lower single doses is probably more favorable for the mother. On the other hand, a shorter time interval between the doses may allow more women in preterm birth to receive the full course of steroids. Further studies are required to answer these questions, and better methods for predicting preterm birth should be determined.

Keywords: Antenatal steroids; Pregnancy; Dexamethasone; Betamethasone; Preterm delivery

Introduction

In 1972, Liggins and Howie [1] demonstrated that antenatal steroid administration reduced the incidence of respiratory distress syndrome (RDS) and perinatal mortality in neonates. Since the publication of these findings, perinatal and long-term results of steroid therapy have been evaluated in numerous studies. Antenatal steroid administration (betamethasone or dexamethasone) has been shown to reduce the risk of the following complications of preterm delivery while not increasing the risk of infections in mothers and neonates: respiratory distress syndrome (RDS) (RR 0.66), intraventricular hemorrhage (IVH) (RR 0.54), necrotizing enterocolitis ( NEC) (RR 0.46), and neonatal death (RR 0.69) [2].

Currently, a single course of steroid therapy including intramuscular administration of 24 mg of steroid over 24 hours is recommended; this includes betamethasone 2 × 12 mg every 24 hours or dexamethasone 4 × 6 mg every 12 hours [3,4].

Numerous studies have compared the effects of the route of administration, the type and the dose of the steroid as well as the timing on perinatal outcomes in neonates and in mothers.

Route of administration

In 1998, a study compared oral (4 × 8 mg every 12 hours) and intramuscular (4 × 6 mg every 12 hours) routes of dexamethasone administration in the reduction of RDS incidence in preterm neonates [5]. The study was discontinued due to the obtained results (170 mothers; 188 fetuses). The authors observed no difference in the incidence of RDS between the groups, but oral administration was associated with an increased risk of IVH (15.9% vs. 3.3%, P = 0.03) and sepsis (15.9% vs. 1.6%, P = 0.009) in neonates. Intravenous dexamethasone was also effective in reducing perinatal mortality from respiratory distress syndrome in premature infants delivered between 28 to 33 weeks gestation [6].

Type of steroid

To date, the dispute of whether betamethasone or dexamethasone should be used has not been solved. Betamethasone is characterized by a longer half-life (12 hours) and is less likely to cause periventricular leukomalacia than dexamethasone [7]. Dexamethasone is characterized by a stronger affinity for steroid receptors and a greater reduction in the risk of IVH while containing potentially neurotoxic sulfonate groups [8].

In the 1990s, several studies were published on the impact of steroid treatment on fetal cardiac function and/or biophysical profile [9-11]. In a double-blind, randomized study, Magee et al. [9] administered 24 mg of betamethasone (2 × 12 mg every 12 hours) or 24 mg of dexamethasone (according to the same dosing regimen) to 59 women in with single pregnancies at risk of preterm delivery. The authors concluded that both steroids led to a reduction in basic fetal heart rate and increased the variability of both short-term and long-term heart function on the first day after administration while reducing fetal heart rate amplitude and potentially causing heart rate deceleration on the
second day after administration. The authors noted that these are physiological effects of the steroids.

In the same year, Dutch authors [11] observed that betamethasone (24 mg; 2 x 12 mg every 24 hours) reduced the acceleration of fetal heart rate and fetal breathing movements. Dexamethasone (24 mg; 2 x 12 mg every 24 hours) led to increased short-term variability on the first day of treatment. All the above changes were unobservable on the fourth day after completion of the treatment. Similar results were obtained by Israeli researchers [12].

A year later, Senat et al. [10] published a study that compared the effects of dexamethasone (4 x 6 mg every 12 hours) and betamethasone (4 x 6 mg every 12 hours) administered intramuscularly to accelerate the maturity of the respiratory system and fetal heart function in a non-blinded randomized study. Computerized cardiotocogram (CTG) parameters obtained before, during and after treatment were compared. No differences were observed between the groups with regard to neonatal outcomes. Reduced fetal heart rate oscillations were observed in the betamethasone group (n=42). The changes resolved within a week after treatment completion. No significant changes were observed in the dexamethasone group (n=40). The authors concluded that steroid treatment should also be accompanied by fetal health assessment methods other than CTG and that dexamethasone should be the medication of choice when steroid treatment is required.

In the next year, the results of a randomized study regarding the impact of steroid therapy on fetal heart function and biophysical profile were published [13]. The study compared the effects of 24 mg of dexamethasone (4 x 6 mg every 12 hours) and 24 mg of betamethasone (2 x 12 mg every 24 hours). Both medications altered the fetal heart function (reduced acceleration, long-term and short-term variability) and biophysical profile (reduced number of fetal movements as well as fetal breathing movements) over 48 hours; the changes were greater following betamethasone administration.

Several years later, Subtil et al. [14] compared the effects of 24 mg of betamethasone acetate and betamethasone phosphate (2 x 12 mg every 24 hours) as well as 24 mg of dexamethasone (4 x 6 mg every 12 hours) on fetal heart function in 105 mothers at risk of preterm delivery. The changes observed by the authors included an increase in oscillations and numbers of fetal movements perceived by the mother during the treatment (day 1) as well as a reduction in oscillations and acceleration after treatment completion (days 2 and 3); the changes were greater following betamethasone administration.

The authors of the aforementioned studies noted that changes in fetal heart function resulting from steroid administration might be the cause of iatrogenic preterm delivery if caution is not exercised.

In 2005, Polish researchers assessed the effects of steroid treatment on the blood flow within the middle cerebral artery of the fetus as well as in the umbilical artery by testing the flow rates before treatment as well as 24 and 72 hours after administration of the first dose [15]. The authors observed that 24 mg of dexamethasone (n=34) delivered intramuscularly (4 x 6 mg every 12 hours) reduced the pulsatility index (PI) within the median cerebral artery (MCA) 72 hours after administration of the first dose while not affecting the PI within the umbilical artery (UA). No changes in the pulsatility index were observed in either the fetal MCA or UA following the administration of 24 mg of betamethasone (n=33)(2 x 12 mg every 24 hours).

According to the results of randomized, double-blind studies to assess the effects of intramuscular administration of 24 mg of dexamethasone (4 x 6 mg every 12 hours) and betamethasone (2 x 12 mg every 24 hours) on the morbidity and mortality of preterm neonates, the latter drug led to more frequent incidence of neonatal IVH (RR 2.97, 95% confidence interval [CI] 1.22–7.24, P=.02) [16].

Danesh et al. [17] compared the effects of 24 mg of dexamethasone (4 x 6 mg every 12 hours) and 24 mg of betamethasone (2 x 12 mg every 24 hours) on maternal inflammatory markers to conclude that in the case of symptoms of preterm labor with PPROM, dexamethasone significantly increased maternal leukocytosis. No differences were observed regarding inflammatory markers in pregnant mothers with preterm labor symptoms and retained amniotic fluid in both groups.

Steroid dosage

The best treatment effects of antenatal steroid administration are observed when the delivery occurs within 7 days from administration of the full steroid dose [2]. After this time, no significant reduction is observed in the incidence of RDS, cerebral hemorrhage or blood breakthrough into the ventricular system [2]. If the delivery is expected to occur before the completion of the full course of steroid treatment, the treatment should be initiated all the same. Even the first dose of betamethasone has been shown to reduce the risk of IVH and neonatal death [18-21].

In 2015, the results of a multicenter study assessing the appropriate use of steroid therapy [22] in 246,459 pregnant patients during 1988-2012 were published. The authors declared that during the study period, the steroid use rates increased from 10 to 23% for optimal drug doses (OR 2.7, 95% CI 1.6-4.5), from 7 to 34% for suboptimal drug doses (OR 6.7, 95% CI 3.9-11.6) and from 0.2 to 1.7% for unquestionably appropriate administration (OR 7.5, 95% CI 4.9-11.3). In addition, 52% of mothers who received steroids gave birth at week 35 or later. Therefore, better methods of predicting preterm birth should be determined.

Khandelwal et al. [23] observed that 24 mg of betamethasone administered as 2 x 12 mg every 24 hours or every 12 hours did not change the risk of RDS (36.5% vs. 37.3%; P = not significant), whereas necrotic enterocolitis developed in neonates born from the group that received the drug at shorter intervals (6.2% vs. 0%; P=0.03).

In a study conducted at our institution comparing the neonatal and maternal results depending on the regimen of administration of 24 mg of betamethasone, i.e., 6 x 4 mg every 8 hours (study group) and 2 x 12 mg every 24 hours (control group), we observed a significant increase in maternal leucocytosis as well as reduced erythrocyte counts, hemoglobin levels and hematocrit in the control group compared with the study group [24]. No differences were observed between the study group and the control group in terms of complications such as moderate or severe respiratory disorders, IVH, NEC, retinopathy, infection, hyperbilirubinemia or anemia in neonates. Mild respiratory disorders were observed more frequently in the study group.

Timing of steroid treatment

The time limit for the use of steroids in pregnancy is also a matter of dispute. In 2011, BMC published the results of a prospective, double-blind randomized study comparing the effects of intramuscular betamethasone administered over two 12-mg doses at a 24 hour interval with placebo on complications occurring in late preterm
neonates (week 34-36.7: 143 in the treatment group vs. 130 in the placebo group) [25]. No differences between groups were observed with respect to the incidence of RDS (1.4% vs. 0.8%; p=0.54) and transient tachypnea (24% vs. 22%; p=0.77) as well as regarding the need for respiratory support (approximately 20% in both groups) and neonatal morbidity (62% vs. 72%; p=0.08). No differences were observed between the groups with regard to the gestational age at delivery, birth weight, 1-minute and 5-minute Apgar scores, surfactant treatment, neonatal intensive care unit (NICU) admissions, or the incidence of sepsis. The groups differed in the incidence of jaundice that required phototherapy (24% in the treatment group vs. 38% in the placebo group; p=0.01).

Kamath-Rayne et al. [26] and Yinon et al. [27] also demonstrated that steroid treatment applied at gestational week 34 and onward did not reduce the morbidity associated with respiratory diseases.

According to the results of a meta-analysis, steroid treatment is beneficial in preterm deliveries when administered by gestational week 34, day 6 [2].

Repetitive dose courses

Because the beneficial effects of steroids wane over time, repeated courses of steroids were routinely used even at the beginning of this century despite the fact that a study demonstrating the unfavorable effects of repeated steroid courses in animals was published in 1995 [28]. The authors demonstrated that repeated courses of steroids might cause intrauterine growth restriction (IUGR), reduced neonatal birth weights, and optic nerve myelination disturbances.

In humans, studies were conducted in this respect only at the beginning of the current century. French et al. demonstrated that repeated administration of steroid doses between gestational weeks 24 and 33 reduced the birth weight and head circumference as well as increased the incidence of aggressive, destructive, and hyperkinetic behavior at a later age (3 and 6 years) [29,30].

In 2008, a Canadian multicenter, double-blind randomized study assessing the effects of repeated doses of steroids on perinatal outcomes was published [31]. Included in the study were 1858 women at gestational weeks 25 to 32 who had received a single course of steroids due to preterm labor and did not gave birth after the following 14-21 days. Due to the continued risk of preterm delivery, the patients received steroid therapy (n=937) (2 × 12 mg at a 24-h interval) or placebo (n=921) every 14 days until the delivery or completion of pregnancy at week 33. In the steroid therapy group, 41% of women received 1 course of treatment, 33% of women received 2 courses of treatment, 16% of women received 3 courses of treatment, and 10% of women received 4 courses of treatment. No differences were observed between the groups with regard to neonatal morbidity and mortality. Neonates subjected to repeated courses of steroid therapy were born with lower birth weights (2216 g vs. 2330 g, p=0.0026), lower body lengths (44.5 cm vs. 45.4 cm, p<0.001) and lower head circumferences (31.1 cm vs. 31.7 cm, p<0.001). No differences were observed between the groups with regard to maternal outcomes.

In 2014, Elfayomy and Almasry [32] also demonstrated that repeated doses of dexamethasone caused lower birth weights, body lengths and head circumferences in neonates as well as lower placental weights in mothers. The authors also observed lowered serum levels of vascular endothelial growth factor (VEGF) in mothers subjected to repeated courses of steroid therapy, leading to reduced placental vascularity (Table 1).

| Study | Year | Number of neonates | Subject | Major findings |
|-------|------|---------------------|---------|---------------|
| Egerman R et al. | 1998 | 188 | 4 × 8 mg every 12 hours oral dexamethasone vs 4 × 6 mg every 12 hours intramuscular dexamethasone | Oral dexamethasone increased risk of neonatal IVH and sepsis |
| Magee LA et al. | 1997 | 59 | 2 × 12 mg every 12 hours betamethasone vs 2 × 12 mg every 12 hours dexamethasone | Both: reduction in basic fetal heart rate and increase the variability of short and long-term heart; reducing fetal heart rate amplitude |
| Wong D et al. | 2014 | 2549 | none, incomplete, complete | Complete course: higher infant survival rates, lower rates of severe IVH and NEC; any exposure: reduces the risk of moderate cerebral palsy |
| Lee BH et al. | 2008 | 1124 | steroid exposure: betamethasone vs dexamethasone vs no steroid exposure | Betamethasone exposure increased likelihood of unimpaired neurodevelopmental status and reduced risk of hearing impairment compared with prenatal dexamethasone exposure or no prenatal steroid exposure |
| Elimian A et al. | 2003 | 229 | 12-mg dose of betamethasone vs no steroid exposure | Incomplete course of steroids reduce the rate of intraventricular hemorrhage, neonatal death and the need for vasopressors |
| Senat MV et al. | 1998 | 97 | dexamethasone vs betamethasone | Betamethasone decreases variability of fetal heart rate |
| Rotmensch S et al. | 1999 | 46 | dexamethasone vs betamethasone | Dexamethasone and betamethasone (more pronounced effect) induce a profound, albeit transient, suppression of fetal heart rate and biophysical activities |
| Mushkat Y et al. | 2001 | 40 | dexamethasone vs betamethasone | Betamethasone induced a significant decrease in fetal movements |
Table 1: Included studies.

| Study                                      | Year | No. | Type of Treatment | Outcome                                                                 |
|--------------------------------------------|------|-----|------------------|--------------------------------------------------------------------------|
| Elfayomy AK et al.                         | 2014 | 71  | single course    | multiple antenatal courses of dexamethasone compromised                   |
| Urban R et al.                             | 2005 | 67  | dexamethasone     | decrease in fetal middle cerebral artery impedance at 72 h after          |
| Porto AM et al.                            | 2011 | 273 | 2 × 12 mg         | steroids at 34-36 weeks of pregnancy does not reduce the incidence of    |
| French NP et al.                           | 2004 | 541 | multiple courses  | multiple antenatal courses of corticosteroids may protect against        |
| Murphy KE et al.                           | 2008 | 1858| multiple courses  | multiple courses do not improve preterm-birth outcomes, and are          |

Conclusions

One should consider the potential benefits of dexamethasone in cases of risk of preterm delivery due to abnormalities in fetal health assessments (abnormal CTG records, reduced biophysical profile). Dexamethasone may also lead to better results when preterm neonates are burdened with cardiovascular defects or diseases. The opposite holds true for abnormal flows within UA or fetal MCA, i.e., one should consider whether betamethasone is the appropriate drug of choice.

- Steroid treatment after 34 weeks of gestation is not beneficial.
- Administration of the full course of steroid treatment (24 mg) in lower single doses is probably more favorable for the mother.
- A shorter time interval between the doses may allow more women in preterm birth to receive the full course of steroids.
- Further studies are required to find better methods for predicting preterm birth.

Considering the benefits and the risks of antenatal steroid treatment, the type and the dosage of prenatal steroid should be determined carefully by the team of physicians, care managers and the patients [33]. That may attribute to the optimal perinatal outcome [34].

References

1. Liggins GC, Howie RN (1972) A controlled trial of antepartum glucocorticoid treatment for the prevention of respiratory distress syndrome in premature infants. Pediatrics 50: 515-525.
2. Roberts D, Dalsied SR (2006) Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev CD004454.
3. Miracle X, Di Renzo GC, Stark A, Fanaroff A, Carbonell-Estrany X, et al. (2008) Guideline for the use of antenatal corticosteroids for fetal maturation. J Perinat Med 36: 191-196.
4. Royal College of Obstetricians and Gynaecologists Green-top Guideline No. 7. (2010) Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality.
5. Egerman R, Mercer B, Doss J, Sibai B (1998) A randomized, controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. Am J Obstet Gynecol 179: 1120-1123.
6. Young BK, Klein SA, Katz M, Wilson SJ, Douglas GW (1980) Intravenous dexamethasone for prevention of neonatal respiratory distress: A prospective controlled study. Am J Obstet Gynecol 138: 203-209.
7. Lee BH, Stoll BJ, McDonald SA, Higgins RD (2008) Neurodevelopmental outcomes of extremely low birth weight infants exposed prenatally to dexamethasone versus betamethasone. National Institute of Child Health and Human Development Neonatal Research Network. Pediatrics 21: 289-296.
8. Brownfoot FC, Crowther CA, Middleton P (2008) Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 4: CD006764.
9. Magee LA, Dawes GS, Moulden M, Redman CW (1997) A randomised controlled comparison of betamethasone with dexamethasone: effects on the antenatal fetal heart rate. Br J Obstet Gynaecol 104: 1233-1238.
10. Senat MV, Minoui S, Multon O, Fernandez H, Frydman R, et al. (1998) Effect of dexamethasone and betamethasone on fetal heart rate variability in preterm labour: a randomised study. Br J Obstet Gynaecol 105: 749-755.
11. Mulder E, Derks J, Visser G (1997) Antenatal corticosteroid therapy and fetal behaviour: a randomised study of the effect of betamethasone and dexamethasone. Br J Obstet Gynaecol 104: 1239-1247.
12. Mushkat Y, Ascher-Landsberg J, Keidar R, CarmonE, Pauzner D, et al. (2001) The effect of betamethasone versus dexamethasone on fetal biophysical parameters. Eur J Obstet Gynecol Reprod Biol 97: 50-52.
13. Rotmensch S, Liberati M, Vine TH, Celetanto C, Ben-Rafael Z, et al. (1999) The effect of betamethasone and dexamethasone on fetal heart rate patterns and biophysical activities. A prospective randomized trial. Acta Obstet Gynecol Scand 78: 493-500.
14. Subtil D, Tiberghien P, Devos P, Therby D, Leclerc G, et al. (2003) Immediate and delayed effects of antenatal corticosteroids on fetal heart rate: a randomized trial that compares betamethasone acetate and phosphate, betamethasone phosphate, and dexamethasone. Am J Obstet Gynecol 188: 524-531.
15. Urban R, Lemancewicz A, Przepies’s J, Urban J, Krętowska M (2005) Antenatal corticosteroid therapy: a comparative study of dexamethasone and betamethasone effects on fetal Doppler flow velocity waveforms. Eur J Obstet Gynecol Reprod Biol 120: 170-174.
16. Elinian A, Garry D, Figueroa R, Spitzer A, Wiencek V, et al. (2007) Antenatal Betamethasone Compared With Dexamethasone (Betacode Trial).
17. Danesh A, Janghorbani M, Khalatbari S (2012) Effects of antenatal corticosteroids on maternal serum indicators of infection in women at risk for preterm delivery: A randomized trial comparing betamethasone and dexamethasone. J Res Med Sci 17: 911-917.
18. Elinian A, Figureoa R, Spitzer AR, Ogburn PL, Wiencek V, et al. (2003) Antenatal corticosteroids: are incomplete courses beneficial? Obstet Gynecol 102: 352-355.
19. Chien LY, Ohiesson A, Seshia MMK, Boulton J (2002) Variations in antenatal corticosteroid therapy: A persistent problem despite 30 years of evidence. Obstet Gynecol 99: 401-408.
20. Wong D, Abdel-Latif ME, Kent A (2012) Differences in mortality/morbidity with a complete course of antenatal steroids compared to an incomplete/no course in extremely premature neonates. Arch Dis Child 97: A348-A349.

21. Wong D, Abdel-Latif M, Kent A, NICUS Network (2014) Antenatal steroid exposure and outcomes of very premature infants: a regional cohort study. Arch Dis Child Fetal Neonatal Ed 99: 12-20.

22. Razaz N, Skoll A, Fahey J, Allen VM, Joseph K5 (2015) Trends in optimal, suboptimal, and questionably appropriate receipt of antenatal corticosteroid prophylaxis. Obstet Gynecol 125: 288-296.

23. Khandelwal M, Chang E, Hansen C, Hunter C, Milcarek B (2012) Betamethasone dosing interval: 12 or 24 hours apart? A randomized, noninferiority open trial. Am J Obstet Gynecol 206: 201.e1-201.e11.

24. Romejko-Wolniewicz E, Oleszczuk L, Zaręba-Szczudlik J, Czajkowski K (2013) Dosage regimen of antenatal steroids prior to preterm delivery and effects on maternal and neonatal outcomes. J Matern Fetal Neonatal Med 26: 237-241.

25. Porto AM, Coutinho IC, Correia JR, Amorim MM (2011) Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. BMJ 342: d1696.

26. Kamath-Rayne BD, DeFranco EA, Marcotte MP (2012) Antenatal steroids for treatment of fetal lung immaturity after 34 weeks of gestation: an evaluation of neonatal outcomes. Obstet Gynecol 119: 909-916.

27. Yinon Y, Haas J, Mazaki-Tovi S, Lapidot N, Mazkereth M, et al. (2012) Should patients with documented fetal lung immaturity after 34 weeks of gestation be treated with steroids? Am J Obstet Gynecol 207: 222e1-222e4.

28. Ballard PL, Ballard RA (1995) Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. Am J Obstet Gynecol 173: 254-262.

29. French NP, Hagan R, Evans SF, Godfrey M, Newnham JP (1999) Repeated antenatal corticosteroids: Size at birth and subsequent development. Am J Obstet Gynecol 180: 114-121.

30. French NP, Hagan R, Evans SF, Mullan A, Newnham JP (2004) Repeated antenatal corticosteroids: effects on cerebral palsy and childhood behavior. Am J Obstet Gynecol 190: 588-595.

31. Murphy KE, Hannah ME, Willan AR, Hewson SA, Olhson A, et al. (2008) Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. Lancet 372: 2143-2151.

32. Elfayomy AK, Almasry SM (2014) Effects of a single course versus repeated courses of antenatal corticosteroids on fetal growth, placental morphometry and the differential regulation of vascular endothelial growth factor. J Obstet Gynaecol Res 40: 2133-2145.

33. Cecere A, Scicchitano P, Zito A, Sassara M, Bux F, et al. (2014) Role of Care Manager in Chronic Cardiovascular Diseases. Ann Gerontol Geriatric Res 1: 1005.

34. Ciccone MM, Aquilino A, Cortese F, Scicchitano P, Sassara M, et al. (2010) Feasibility and effectiveness of a disease and care management model in the primary health care system for patients with heart failure and diabetes (Project Leonardo). Vasc Health Risk Manag 6: 297-305.