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Objectives: Gestational Diabetes Mellitus (GDM) is a pregnancy-induced Impaired Glucose Tolerance (IGT) and insulin resistance occurs and diagnoses during pregnancy and gradually disappears after delivery. A mild to moderate physical activity is suggested as an adjuvant treatment for GDM; in addition, aerobic and resistance trainings might be effective in preventing or controlling GDM in the different manners. The current study aimed at comparing aerobic and resistance trainings plausible effects on insulin resistance and homeostasis model assessment of β-cell function in females with GDM.

Materials & Methods: A total of 34 females with GDM at 24th week of pregnancy undergoing insulin treatment were enrolled and randomly assigned into 3 groups; 12 subjects participated in an aerobic training program (3 day/week, 30 to 45 minute/day, 50% to 70% maximum Heart Rate (HR)), 11 patients participated in a resistance training (3 day/week, 2 to 3 minutes set of 15 repetitions, 50% to 70% maximum HR), and 11 participants comprised the control group and not participated in any exercise program. Fasting blood samples were obtained from the subjects to assess clinical parameters.

Results: The results of covariance analysis indicated a significant difference on insulin plasma levels (P=0.031) and insulin resistance index (the homeostasis model assessment-estimated insulin resistance (HOMA-IR) (P=0.008) among the groups. The resistance training program significantly reduced the level of fasting blood sugar (P=0.031) and increased HOMA-β (P=0.031).

Conclusion: The exercise can offer a different method to patients with GDM, which benefit from several molecular pathways, and also can be proposed as a framework to design effective GDM treatment regimens and prevention programs. However, further consecutive studies are required in order to achieve the deeper and conclusive findings and obtain the mechanisms underlying the changes on the GDM acquired by exercise.
1. Introduction

Gestational Diabetes Mellitus (GDM) is a pregnancy-induced Impaired Glucose Tolerance (IGT) and insulin resistance occurs and diagnoses during pregnancy and gradually disappears after delivery [1]. Compensating for IGT, pancreatic β-cells physiologically increase the insulin secretion; however, when pancreatic β-cell function is lower than normal, secretion may not be enough for compensation and causes GDM. Thus, the robust plasticity of β-cell function regulating the progressive insulin resistance is the trademark of normal glucose regulation during the pregnancy [2, 3].

GDM might cause an abnormal increase in the livers’ glucose production and reduces the muscles and adipose tissues glucose uptake [1]. GDM, even in a mild course of the disease, is related to numerous complications during pregnancy and delivery comprising preeclampsia, prolonged labor, the higher rate of cesarean section, macrosomia, cephalopelvic disproportion, uterine rupture, shoulder dystocia, and perineal laceration [4-7]. In addition, it increases the risk for long-term complications for the mother and fetus including obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM) [8-12].

Therefore, glycemic control of patients with GDM is required to minimize complications. In this respect, diet therapy is the first-line therapy that is accompanied by insulin therapy in severe GDM cases, although the aggressive use of insulin might increase the incidence of Small-for-Gestational-Age (SGA) infants [13]. Nowadays, the positive role of exercise and physical activity in prevention and control of different diseases was verified. Muscle contractions increase the AMP/ATP and creatinine/phosphocreatine ratios, which quickly activate Adenosine Monophosphate Kinase 1 (AMPK1). AMPK is a key intermediary in fatty acid oxidation and glucose transportation in mammalian cells. In skeletal muscle cells, AMPK increases Glucose Transporter (GLUT-4) expression, which in turn, increases GLUT4 translocation rate into the skeletal muscle cells and rises insulin responsiveness of muscle [2, 14].

Contrasting disbelief in physical activity during pregnancy in a few decades ago, a mild to moderate physical activity is suggested as an adjuvant treatment for GDM [13-16]; it even provides benefits to females with GDM that have problem in insulin uptake [17-21]. For instance, participating in any kind of physical activity during the first 20 weeks of pregnancy declines the risk of GDM by about 50% [15]. Aerobic exercises prevent weight gain and maintain cardiovascular fitness [13]. It might lower the blood glucose levels consistently in GDM. Interestingly, an aerobic exercise program 3 times per week can eliminate the need for insulin therapy in females with GDM [19].

In the meantime, it seems that aerobic resistance training is increasingly portraying itself as a suitable method to improve the general health and metabolism, and reduce the risk of diabetes or control the complications. Resistance training, by up-regulation of GLUT4 expression and activating several molecular pathways, increases the glucose intake and muscle strength and mass [19, 21-23]. Thus, due to the importance of pregnancy period, reduced physical activity during pregnancy, and increased prevalence of GDM, and owing to the different mechanisms of resistance and aerobic exercise in diabeties, the current study aimed at comparing the effects of these types of exercises on GDM.

2. Materials and Methods

Participants

In the current interventional study, all the mothers with GDM attending routine visits to the Perinatology Clinic of Hafez Educational Hospital and Motahari Clinic, Shiraz, Iran, affiliated to University of Medical Sciences (Shiraz University of Medical Sciences) from November 2014 to January 2015 were enrolled. Thirty-four inactive pregnant females with GDM at 24th week of pregnancy undergoing insulin therapy were enrolled and randomly assigned to 3 groups of resistance training, aerobic training, and the control. Patients with history of physical activity and systemic diseases within the last year, and the ones with medical complications were excluded from the study.

Gestational Age (GA) of the subjects was calculated based on the first day of the last menstrual period (LMP) and the ultrasound images of the early stages of the pregnancy. The current study was registered in the Iranian Registry of Clinical Trials (IRCT code: 2014031717035). All the subjects signed the written informed consent form prior to intervention.

Material and Procedures

The participants were asked to complete a questioner including their physical activity status, using the authentic International Physical Activity Questionnaires (IPAQ), demographic information, and medical history.
The experimental groups spent a 6-week exercising program, while the control group did not participate in any training program. All subjects performed the exercises under the supervision of the senior author. According to the guidelines for exercise during pregnancy and characteristics of aerobic and resistance training programs, a 6-week personal training program, 3 days a week with moderate intensity (maximum Heart Rate (HR) of 50% to 70%) was scheduled [15-24].

The aerobic training started from 30-minute session and gradually increases to 45 minutes in the last sessions. The training program comprised of general warm-up, non-water-based stretching exercises and slow walking in water, water-based aerobic exercises with moderate intensity and then slowly walking towards recovery [1, 15, 19]. To perform resistance training, an elastic band exercises as well as circuit-type resistance training were used in order to elaborate main muscle groups (chest, back, biceps, triceps, deltoid, quadriceps, thigh, and calf muscles). A circuit series was scheduled as a sequence of the mentioned 8 exercises (stations). The subjects performed each exercise for 15 times (station) with a minimum resting period of 30 seconds and a maximum of 1 minute intervals. During the first 2 weeks of the study, the subjects underwent 2 circuit series, continued by 3 circuit series until the end of the study [24].

The intensity of trainings was controlled based on the Rated Perceived Exertion (RPE) scale (Polar heart rate monitor, Finland). The 6-20 point Borg RPE scale was recommended with 12 to 14 (a rate of 13 corresponded to “somewhat hard”) as the RPE range to apply in pregnancy. Hence, 90 minutes after the meal, before training, sample blood glucose level was measured by a glucometer; if glucose level ranged 100 to 250 mg/dL, the participant could attempt exercise [21, 24].

Clinical assessments

At the baseline, the height and weight of each participant were measured and the Body Mass Index (BMI) was calculated. Twenty-four hours before the initiation of training, a fasting blood sample was taken from the subjects, between 7:00 and 8:00 AM, to determine the baseline blood values. Forty-eight hours post-training, blood assessments were repeated to determine any plausible changes.

In order to measure blood parameters, venous blood samples were taken while fasting. The blood samples were centrifuged and after 2-3 hours, the serum glucose level was measured by the glucose oxidase method (Hitachi auto-analyzer and Pars Azmoon kits). The serum insulin level was measured by the Enzyme-Linked Immunosorbent Assay (ELISA) technique (IZOTOPES Ltd Company, Hungary). Homeostasis Model Assessment–Insulin Resistance (HOMA-IR) was calculated as fasting glucose (mg/dL) multiplied by fasting insulin (µU/ml) divided by 405. Homeostasis model assessment of β-cell function (HOMA-β), an insulin secretion index, was calculated as 360 multiplied by fasting insulin (µU/ml) divided by (fasting glucose (mg/dL)).

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of data. Considering the small sample size in each group, some variables were not distributed normally; thus, non-parametric Wilcoxon sign-rank test was employed instead of the paired t test. Analysis of Covariance (ANCOVA) was applied for intergroup comparisons. Data was analyzed using the SPSS version 23. P≤0.05 was considered as level of significance.

3. Results

The patients’ descriptive statistics depicted in Table 1 showed no differences among 3 groups at the baseline. Table 2 shows changes in clinical parameters during the study and comparisons among the groups. According to Table 2, fasting sugar levels reduced during the 6-week training, while the difference between the baseline and post-training levels was statistically significant in the resistance training group (P=0.012). Regarding the insulin levels, an insignificant decrease was observed in the aerobic group and insignificant increase was shown in the resistance and control groups.

Furthermore, HOMA-IR showed an insignificant decrease in both training groups, and an insignificant increase in the control group. It was also found that HOMA-β significantly increased in the resistance group (P=0.032), but an insignificant reduction was observed in the aerobic and control groups. The analysis of covariance showed that the HOMA-IR and insulin levels were statistically significant in terms of intergroup differences (P=0.031, 0.008).

4. Discussion

Pancreatic β-cell dysfunction, which accounts for a chronic defect, is one of the main pathological mechanisms involving in GDM. Although it is likely to precede the pregnancy, is primary detected clinically in the form of insufficient β-cell compensation for insulin resistance at the late pregnancy, and even presents in postpartum period [2].
One of the hallmarks of the pregnancy period is the increased insulin resistance, which becomes much more important in GDM, due to the dangerous short- and long-term complications for both mother and fetus [3]. Apparently, GDM in females with normal weight is somewhat due to defects in pancreatic β-cells, which does not get better by exercise; while in females with overweight, insulin resistance might be the prominent mechanism. Evidence showed that the exercise protective effects on T2DM or GDM are more among individuals with obesity who are at risk for insulin resistance [25-27].

Insulin resistance during a normal pregnancy is multifactorial and includes reduced ability of insulin to phosphorylate insulin receptors, decreased expression of Insulin Receptor Substrate (IRS-1), and increased P85α.

### Table 1. Patients’ demographic and medical data at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aerobic</th>
<th>Resistance</th>
<th>Control</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>28.92±3.6</td>
<td>30.27±4.149</td>
<td>29.18±4.33</td>
<td>0.701</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.3±3.31</td>
<td>166.27±4.60</td>
<td>162.72±2.61</td>
<td>0.804</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.58±6.96</td>
<td>73.18±10.10</td>
<td>63.81±11.21</td>
<td>0.076</td>
</tr>
<tr>
<td>Pre-pregnancy BMI (kg/m²)</td>
<td>25.36±1.73</td>
<td>26.37±2.41</td>
<td>24.2±3.82</td>
<td>0.154</td>
</tr>
<tr>
<td>Amount of required insulin (u/kg)</td>
<td>0.5±0.23</td>
<td>0.6 ±0.28</td>
<td>0.61±0.04</td>
<td>0.468</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index

* Level of significance: P<0.05

Data are expressed as mean±standard deviation.

### Table 2. Changes in clinical parameters during the intervention in the study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Groups</th>
<th>Pretest</th>
<th>Posttest</th>
<th>Δ</th>
<th>P</th>
<th>Analysis of Covariance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>Aerobic</td>
<td>83.4±8.42</td>
<td>81.75±6.89</td>
<td>-1.9%</td>
<td>0.311</td>
<td></td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>Resistance</td>
<td>93.81±8.19</td>
<td>87.09±8.17</td>
<td>-7.1%</td>
<td>0.012</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>89.54±10.23</td>
<td>89±10.50</td>
<td>-</td>
<td>0.399*</td>
<td></td>
</tr>
<tr>
<td>Insulin (MIU/mL)</td>
<td>Aerobic</td>
<td>8.14±2.82</td>
<td>7.81±2.54</td>
<td>-4.05%</td>
<td>0.685</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resistance</td>
<td>9.81±2.32</td>
<td>10.22±2.76</td>
<td>4.18%</td>
<td>0.431</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>12.54±3.14</td>
<td>13.81±2.90</td>
<td>10.1%</td>
<td>0.149</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Aerobic</td>
<td>1.69±0.58</td>
<td>1.57±0.54</td>
<td>-7.1%</td>
<td>0.486</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resistance</td>
<td>2.26±0.51</td>
<td>2.18±0.58</td>
<td>-3.54%</td>
<td>0.503</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2.76±0.69</td>
<td>3.01±0.60</td>
<td>9.06%</td>
<td>0.169</td>
<td></td>
</tr>
<tr>
<td>HOMA-β</td>
<td>Aerobic</td>
<td>166.92±77.39</td>
<td>180.64±170.9</td>
<td>8.21%</td>
<td>0.594</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resistance</td>
<td>129.11±70.44</td>
<td>177.33±99.7</td>
<td>38.9%</td>
<td>0.032</td>
<td>0.438</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>210.39±129.98</td>
<td>224.17±163.1</td>
<td>6.54%</td>
<td>0.068</td>
<td></td>
</tr>
</tbody>
</table>

* The Wilcoxon sign-rank test was used.

Level of significance: P<0.05

HOMA-IR: the Homeostasis Model Assessment-estimated Insulin Resistance

HOMA-β: the Homeostasis Model Assessment for beta cell function
subunit from Inositol-3-phosphate (PI-3) kinase. In this regard, IRS-1 reduces more in females with GDM and creates higher resistance. However, in females with gestational diabetes, mutual and reverse changes occur at the phosphorylation level of IR and IRS-1 serine and tyrosine, signaling is blocked, GLUT-4 translocation substantially decreases, and less cellular glucose uptake occurs compared with a normal pregnancy [28].

The present study showed that HOMA-β increased in all 3 groups; however, the difference between baseline and end-of-intervention values was significant only in the resistance group. Also, HOMA-IR decreased following the 6 weeks of aerobic and resistance trainings, although the difference was insignificant; the changes in insulin resistance could be used as an argument for the effectiveness of physical activity in gestational diabetes. Evidence on exercise preventive effect before and during the pregnancy mainly rely on the results of cohort studies and a small number of Randomized Controlled Trials (RCT). There was only 1 RCT on the preventive effect of exercise on GDM and insulin resistance in healthy pregnant females [30]. Although the sample size was large (N=855), only 55% of the subjects were assigned to the experimental group (N=375) to follow the recommended exercise regimen, a 12-week exercise program during the second half of pregnancy. Pregnancy outcomes were similar in both groups and the authors concluded that exercise may not prevent GDM or improve insulin resistance.

Two other trials investigated the effect of exercise on insulin resistance as well as blood glucose and insulin levels in healthy pregnant females [30, 31]. However due to the small sample size, the results were not reliable. Hopkins et al. [31] did not find a statistically significant difference in maternal insulin sensitivity in late gestation between control and exercise group. But Callaway et al. [30] found a statistically significant difference in fasting glucose and insulin levels between the 28th and 36th weeks of pregnancy.

In the current study, no significant decline on fasting glucose levels was observed in the aerobic and control groups, but there was a significant decrease in the resistance group. A study by Oostdam et al. [32] showed that an exercise program in the second and third trimesters of pregnancy had no significant effects on fasting blood sugar level and insulin sensitivity in females with overweight who developed GDM. Additionally, Jovanovic-Peterson et al. [33] showed that females who exercised 3 times a week had significantly lower fasting and postprandial blood sugar levels compared with the diet therapy group.

The ability of insulin to prevent lipolysis decreases in the final months of pregnancy and this is even higher in females with GDM; therefore, it leads to increased Free Fatty Acids (FFA), hepatic glucose production, and insulin resistance [22]. The resistance training increases the access to glucose by increasing FFA without any changes in muscle inherent capacity responding to the insulin. While an aerobic training increases the glucose access independent to the changes in FFA, fat mass, and the maximum oxygen intake, which indicates internal changes in muscle glucose metabolism [24]. Probably, due to higher access to FFA, the resistance training showed a significant effect on fasting glucose level in the present study.

The insulin level was insignificantly diminished in the aerobic group, and increased in the resistance and control groups. Marcelo et al. [24] showed that the resistance training causes less insulin consumption in the females with GDM, unlike the results of Brankston et al. [25]. The puzzling results might be due to the patients’ characteristics variability, interventions, exercises duration, and the low number of participants comprising each group. In the present study, unpredictable factors such as mother’s concern on fetus health, physical limitations, and lack of the required energy and motivation could influence the results. There are a few studies dealing with the mechanisms and beneficial effects of exercise on GDM. But, in spite of similarities between GDM and T2DM, their mechanisms are in line. Two routes lead to glucose transportation: the stimulation by insulin and activation by contraction or hypoxia [1]. PI3 kinase intervenes in insulin route, while AMPK participates in the contraction route activation [33].

5. Conclusion

In conclusion, exercise can offer a different method to patients with GDM through several molecular pathways; it might be proposed as a framework for designing effective GDM treatment and prevention programs. However, since the present study was a pioneer in the effect of physical activity on pregnant females with GDM who were in the second trimester, further consecutive studies are recommended in order to achieve deeper and conclusive findings and understand the mechanisms underlying changes on GDM acquired by exercise.

Acknowledgments

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authors acknowledge their gratitude to the authorities of the university for cooperation and support. They also express their appreciation to everyone who cooperated with the project, especially the very dear mothers.

Conflict of Interest

The authors declared no conflicts of interest.

References


Reaching 2016 EAU guideline testosterone level of < 20 ng/dl in the vast majority of patients

Presentations: ELIGARD™ 7.5 mg, 22.5 mg powder and solvent for solution for injection, Composition: ELIGARD™ 7.5 mg One pre-filled syringe (Syringe B) contains 7.5 mg leuprolide acetate. The other ingredients are Poly 0L-cysteic acid copolymer (GS05) and Hydroxyethyl-2-pyrrolidone in the pre-filled syringe with solution for injection (Syringe A) ELIGARD™ 22.5 mg. The active substance is leuprolide acetate. One pre-filled syringe (Syringe B) contains 22.5 mg leuprolide acetate. The other ingredients are Poly 0L-cysteic acid copolymer (GS05) and Hydroxyethyl-2-pyrrolidone in the pre-filled syringe with solution for injection (Syringe A). Indications: ELIGARD™ is indicated for the treatment of hormone dependent advanced prostate cancer and for the treatment of high risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy. Posology and method of administration: Posology Adult Male ELIGARD™ should be administered under the direction of a healthcare professional having available the appropriate expertise for monitoring the response to treatment. ELIGARD™ is administered as a single subcutaneous injection every month for 7.5 mg and every 3 months for 22.5 mg. The injected solution forms a solid medicinal product delivery depot and provides continuous release of leuprolide acetate for 1 or 3 months accordingly. As a rule, therapy of advanced prostate cancer with ELIGARD™ entails long-term treatment and therapy should not be discontinued when remission or improvement occurs. ELIGARD™ may be used as neoadjuvant or adjuvant therapy in combination with radiotherapy in high risk localised and locally advanced prostate cancer. As lack of efficacy may result from incorrect preparation, reconstitution, or administration, testosterone levels should be evaluated in cases of suspected or known handling errors. Method of administration ELIGARD™ should be prepared, reconstituted and administered only by healthcare professionals who are familiar with these procedures. Contraindications: ELIGARD™ is contraindicated in women and in male patients with hypersensitivity to leuprolide acetate, to other GnRH agonists or to any of the excipients in patients who previously underwent orchidectomy (as with other GnRH agonists, ELIGARD™ does not result in further decrease of serum testosterone in case of surgical castration). As sole treatment in prostate cancer patients with spinal cord compression or evidence of spinal metastases. Special warnings and special precautions for use: Lack of clinical efficacy may occur due to incorrect reconstitution of the product. Androgen deprivation therapy may prolong the QT interval. Leuprolide acetate, like other GnRH agonists, causes a transient increase in serum concentrations of testosterone, dihydrotestosterone and acid phosphatase during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms including bone pain, neuropathy, haematuria, or urethral or bladder outlet obstruction. These symptoms usually subside on continuation of therapy. Additional administration of an appropriate androgen should be considered beginning 3 days prior to leuprolide therapy and continuing for the first two to three weeks of therapy. This has been reported to prevent the sequelae of an initial rise in serum testosterone. Cases of urothelial obstruction and spinal cord compression, which may contribute to paraplegia with or without fatal complications, have been reported with GnRH agonists. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted. Patients with ventricular and/or atrio ventricular block as well as patients with urinary tract obstruction should be closely monitored during the first few weeks of therapy. A proportion of patients will have tumors which are not sensitive to hormone manipulation. Absence of clinical improvement despite adequate testosterone suppression is diagnostic of this condition, which will not benefit from further therapy with ELIGARD™. Decreased bone density has been reported in the medical literature in men who have had orchidectomy or who have been treated with a GnRH agonist. Antandrogen therapy significantly increases the risk for fractures owing to osteoporosis. The risk for fractures owing to osteoporosis is generally higher than the risk for pathological fractures. During long-term surveillance, rare cases of pulmonary atelectasis in clinical syndrome secondary to infarction of the pulmonary pleurys have been reported after the administration of GnRH agonists, with a major occurring within 2 weeks of the first dose, and come within the first hour. Hyperglycaemia and diabetes, hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Cardiovascular diseases: Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with a cardiovascular risk factors when determining a treatment for patients with prostate cancer. Special precautions for disposal and other handling Allow the product to come to room temperature by removing from the refrigerator approximately 30 minutes prior to use. Please prepare the patient for injection first, followed by the preparation of the product, using the instructions below. If the product is not prepared using the proper technique, it should not be administered, as lack of clinical efficacy may occur due to incorrect reconstitution of the product. Interaction with other medicinal products and other forms of interaction: No pharmaco genetic drug-drug interaction studies have been performed with ELIGARD™. There have been no reports of any interactions of leuprolide acetate with other medicinal products. Since androgen deprivation treatment may prolong the QT interval, the concurrent use of ELIGARD™ with medicinal products known to prolong the QT interval or medicinal products able to induce toradon de points such as class Ia (eg: quinidine, disopyramide or class III (eg: amiodarone, sotalol, dofetilde), flecainide amphotericin or medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated. Undesirable effects: Adverse reactions seen with ELIGARD™ are mainly subject to the specific pharmacological action of leuprolide, namely increases and decreases in certain hormone levels. The most commonly reported adverse reactions are hot flashes, malaise, nausea and fatigue and transient local irritation at the site of injection. Mild or moderate hot flashes occur in approximately 58% of patients. The following adverse events were reported during clinical trials, with ELIGARD™ patients with advanced prostate carcinoma. Very common: hot flashes, ejaculation, erythema, fatigue, injection site burning, injection site pain, injection site induration, injection site itching. Common: asthenia, diarrhoea, depression, neutropenia, increased blood pressure, prolonged coagulation time, menses, injection site pain, injection site oedema, injection site swelling, impotence, Legal Category: Hospital use only. Marketing Authorisation Holder: Behestan Darou Co. (B.D.) - Astellas Iran office. Date of Preparation: July 2016. Adverse events should be reported. Report adverse events to the Iran regulatory authority and Behestan Darou (B.D.) - No. 10, Behestan Blvd., Pardis K. Moshavar St., Tehran 3959262333, Iran. Reference: SANC version March 2015, FSA revison July 2016.