ABSTRACT

OBJECTIVES: To assess the therapeutic outcomes of infertile patients with insulin resistance

SETTING: A private office of reproductive endocrinology and infertility.

SUBJECTS STUDIED: Consecutive infertile patients (n=83) with overweight (BMI=25-30), obesity (BMI>30) or normal weight (BMI<25) with the baseline (day 2-3 of the cycle) ultrasound exam suggestive of polycystic ovaries were evaluated for their metabolic disorders by 3-hour GTT, measuring glucose and insulin levels in each blood samples.

METHODS: Patients with metabolic disorders, such as insulin resistance (IR), impaired glucose tolerance (IGT) and/or diabetes mellitus (DM) were subjected to a period (>3 months) of lifestyle adjustment, which includes a balanced low-carbohydrate/low-fat diet, regular gentle enduring exercise and stress management, emphasizing mind/body relaxation. Patients with obvious metabolic disorder were placed on insulin sensitizing agents, such as biguanides (metformin) and/or thiazolidinediones (pioglitazone, rosiglitazone) to control blood insulin and glucose levels. Patients with endocrine disorders (e.g. thyroid, prolactin or adrenal androgen excess), anatomical (uterine and/or tubal) factors, and male factor were corrected if possible prior to subject them to ovulation induction or ovulation enhancement therapy. Only a few patients went through IVF program. The results of the therapeutic outcomes, including reproductive as well as metabolic outcomes were evaluated after one year of follow-up.

RESULTS: IR, IGT and DM were more frequently observed in obese patients (BMI>30, n=48) (91.8%, 14.2% and 22.4% respectively) than in non-obese patients (BMI<30, n=34) (58.8%, 0.0% and 5.9% respectively). Lifestyle adjustment and insulin sensitizing agents effectively controlled the insulin and glucose levels within the first 3 months in most patients, and 75.8% of patients lost weight. Among the patients with follow-up more than 3 months (n=62), the pregnancy rate and live-birth rate were higher in the non-obese group (n=23) (78.3% and 94.4%) than in the obese group (n=39) (46.2% and 83.3%); while abortion rate was lower in the non-obese group (5.6%) as compared to the obese group (16.7%). When comparing the patients with IR (n=54) vs. non-IR (n=8), pregnancy rate, live-birth rate and abortion rate were similar between two groups. (IR group: 51.9%, 89.3%, 10.7%; non-IR group: 100%, 87.5%, 12.5% respectively). The cumulative pregnancy rate of all patients at 3 months, 6 months and 12 months were 24.2%, 49.1% and 78.3%.

CONCLUSIONS: Lifestyle adjustment with or without insulin sensitizing agents can effectively improve IR and weight problem, and likely correct ovulatory dysfunction, leading to highly successful reproductive outcomes.

INTRODUCTION

Insulin Resistance (IR) has been frequently associated with polycystic ovaries syndrome (PCOS). Infertile women with PCOS were known to fair poorly in the conventional infertility therapy as well as in the assisted reproductive technologies. The currently available insulin sensitizing agents, such as metformin and thiazolidinediones, seem to improve the therapeutic outcomes of women with PCOS and IR. Insulin resistance occurs frequently in obese persons and it was also known to be associated with chronic stress, regardless of weight condition. Therefore a program emphasizing weight loss and stress management may play significant role in the long term success of correcting IR and even PCOS.

METHODS

SETTING: A private office of reproductive endocrinology and infertility

SUBJECTS STUDIED: Consecutive infertile patients (n = 83) with:
Over Weight: (BMI=25-30), n=16 **Obesity:** (BMI>30), n=49 **Non-Obese**: (BMI=<30), n=34.
Normal weight: (BMI <25) with PCO*, n = 18 [* U/S: >5 small follicles (<7 mm) in Each ovary]

METHODS: Each patient had testing for:
Endocrine profile: Prolactin, Thyroid function tests, DHEA-sulfate, Testosterone
HSG and/or **Laparoscopy** to assess tubal and uterine factor
Lipid profile: Total cholesterol, Triglycerides, HDL & LDL cholesterol
Glucose Tolerance Test (GTT) [100 Gm. Glucose load, blood at Fasting, 1st, 2nd & 3rd hr. Glucose & Insulin]
Male partner: Semen analysis & Endocrine profile plus FSH, LH

Criteria for Diagnosis:

Normal Ranges for Glucose & Insulin Levels in GTT:

	Fasting	1st Hr.	2nd Hr.	3rd Hr.
Glucose (mg/dL)	<105	<200	<160	<120
Insulin (uU/mL)	<25	<110	<80	<50

Diagnosis:

Insulin Resistance (IR): one or more abnormal insulin level
Impaired Glucose Tolerance (IGT): one abnormal glucose level
Diabetes Mellitus (DM): two or more abnormal glucose level

METHODS (continued)

INITIAL CONSULTATION: (***Lifestyle adjustment first, Medicine second***)

Lifestyle adjustment:

Diet: Low ***carbohydrate***, low Calories (<1500 Cal./day). avoid snack and sweet dessert

Protein: low red meat, take poultry, encourage seafood (esp. Fish).

Fat: low fat food, olive oil (instead of vegetable oil) for cooking.

Supplement: Multivitamins,+ extra Vitamin C,Vitamin E & Omega-3 fatty acids.

Exercise: regular (daily), gentle and long-enduring exercise (treadmill, aerobic work-out, dancing or Yoga, Tai-Chi QiGong if available). Avoid strenuous exercise.

Stress management: enjoy family life, deal with stress at work, find hobby p.r.n., Long prayer (for religious) or meditation (for non-religious) before sleep.

Medicine: Metformin (Glucophage 500 mg b.i.d to t.i.d) for IR and DM

Thiazolidinediones (i.e. Actos 15-45 mg/day or Avandia 2-8 mg/day) for DM.

FERTILITY THERAPY: deferred 2-3 months before fertility therapies, & ARTS in later stage.

Infertility Factors: *Endocrine disorders*: corrected and followed at the same time.

Tubal and Uterine Factor: corrected if possible before the fertility therapy.

Male factor: referred to male infertility specialist, and consider IUI etc.

FOLLOW-UP:

Metabolic disorders: return q.2-3 months to reassess the progress.

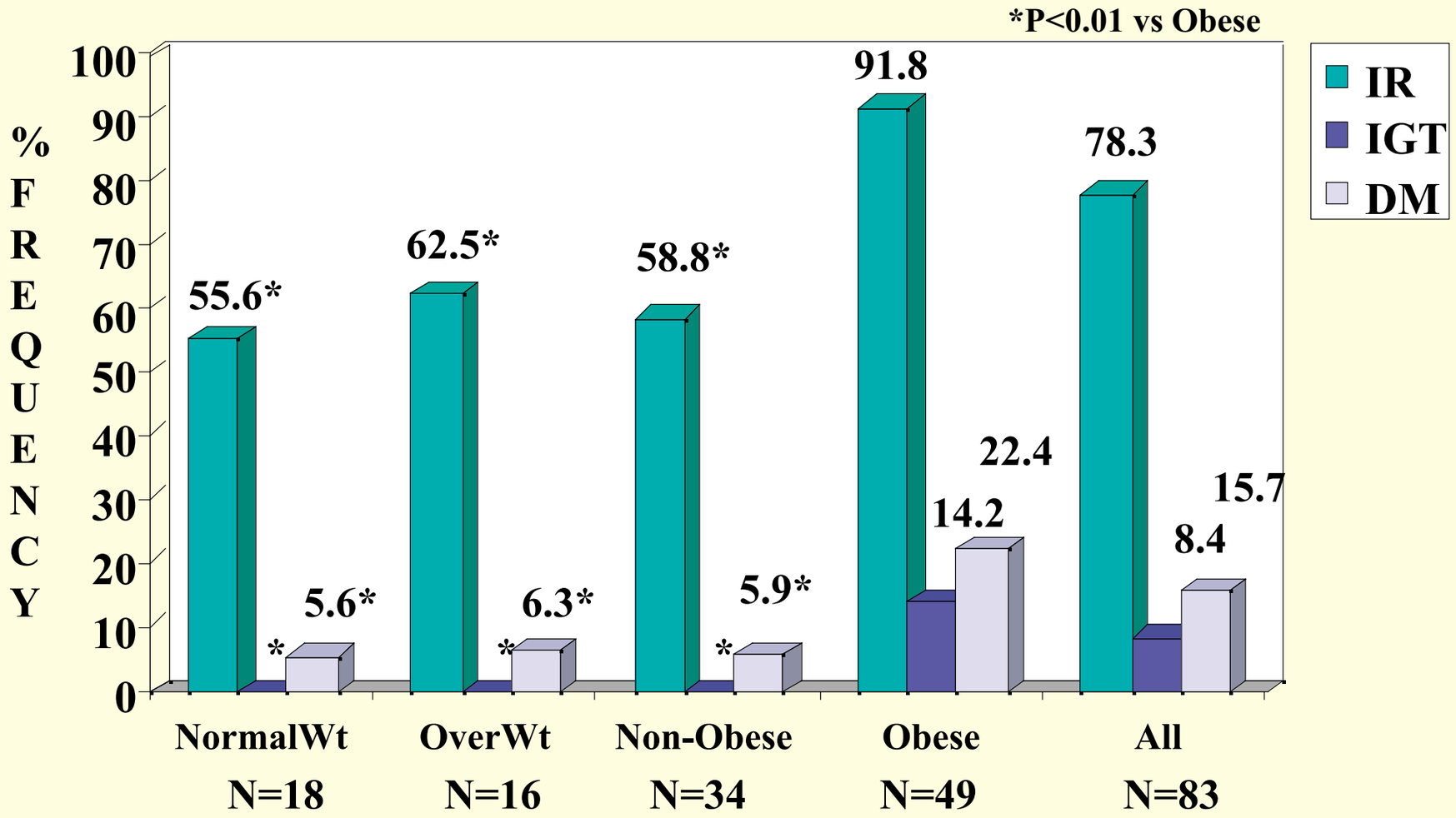
Fertility therapy: return as often as needed.

FREQUENCY OF INFERTILITY FACTORS

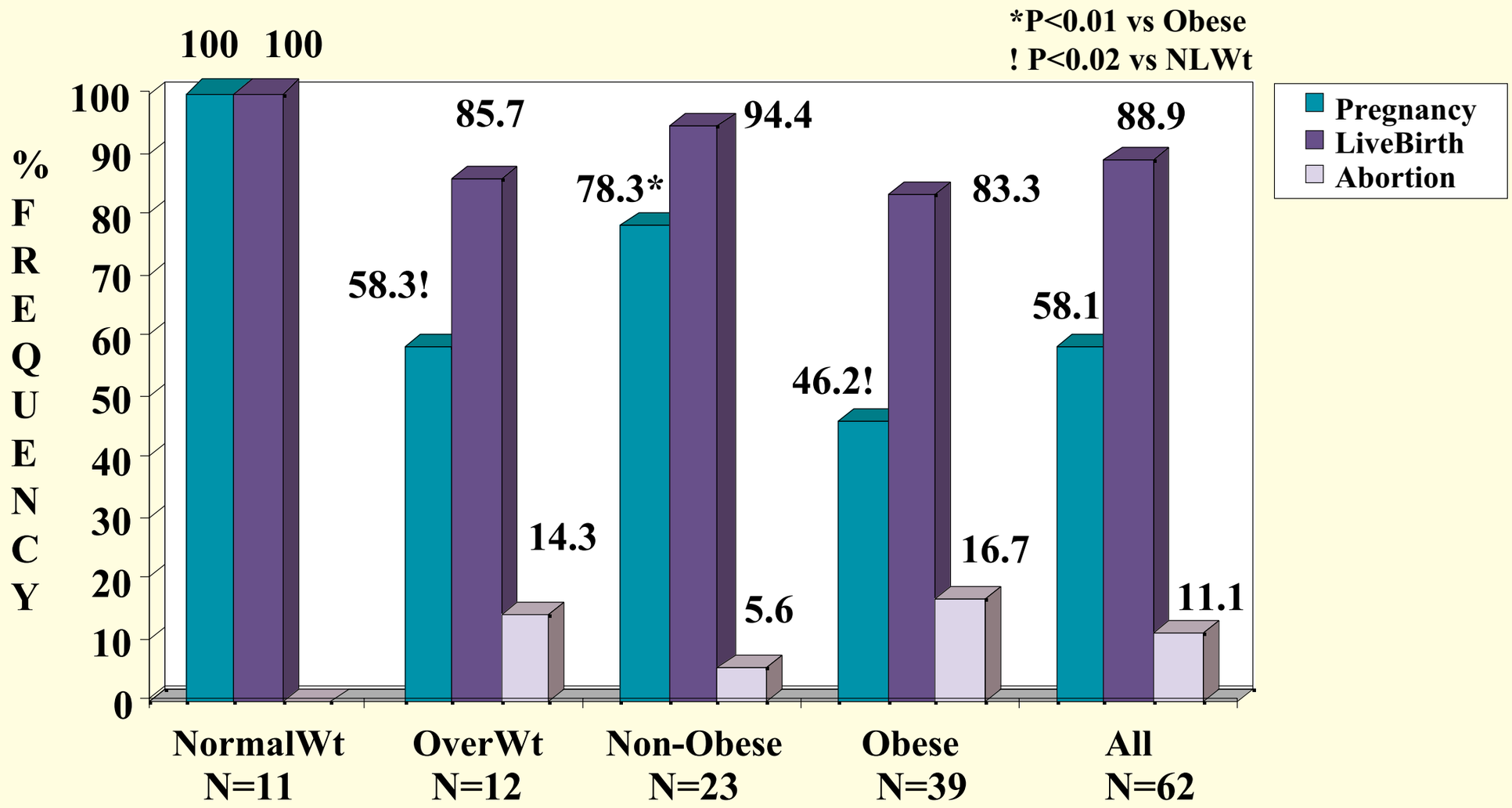
Infertility Factor	Normal Weight	Over-Weight	Obesity	All
(Pt. #)	(18)	(16)	(49)	(83)
Primary Inf.	9 (50%)	9 (56%)	25 (51%)	43 (52%)
Secondary Inf.	9 (50%)	7 (44%)	24 (49%)	24 (48%)
Endocrine F.*	18 (100%)	16 (100%)	49 (100%)	83 (100%)
Tubal F.	1 (5.5%)	3 (19%)	5 (10%)	9 (11%)
Rec.Preg.Loss	1 (5.5%)	2 (13%)	5 (10%)	8 (9.6%)
Male Factor	6 (33%)	6 (38%)	8 (16%)	20 (24%)

* **Endocrine F.:** Metabolic disorders are included in this category.

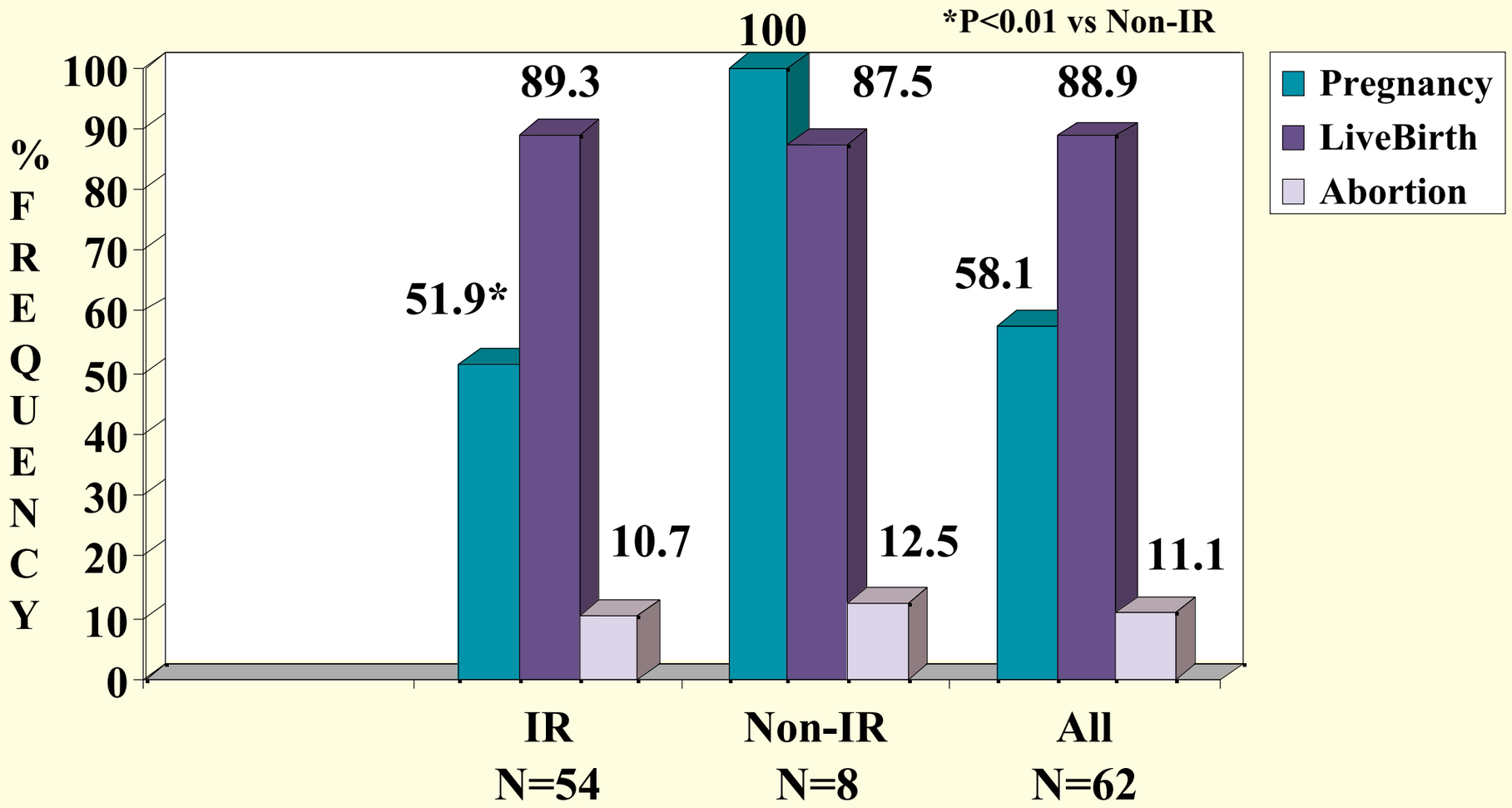
METABOLIC DISORDERS IN INFERTILE PATIENTS



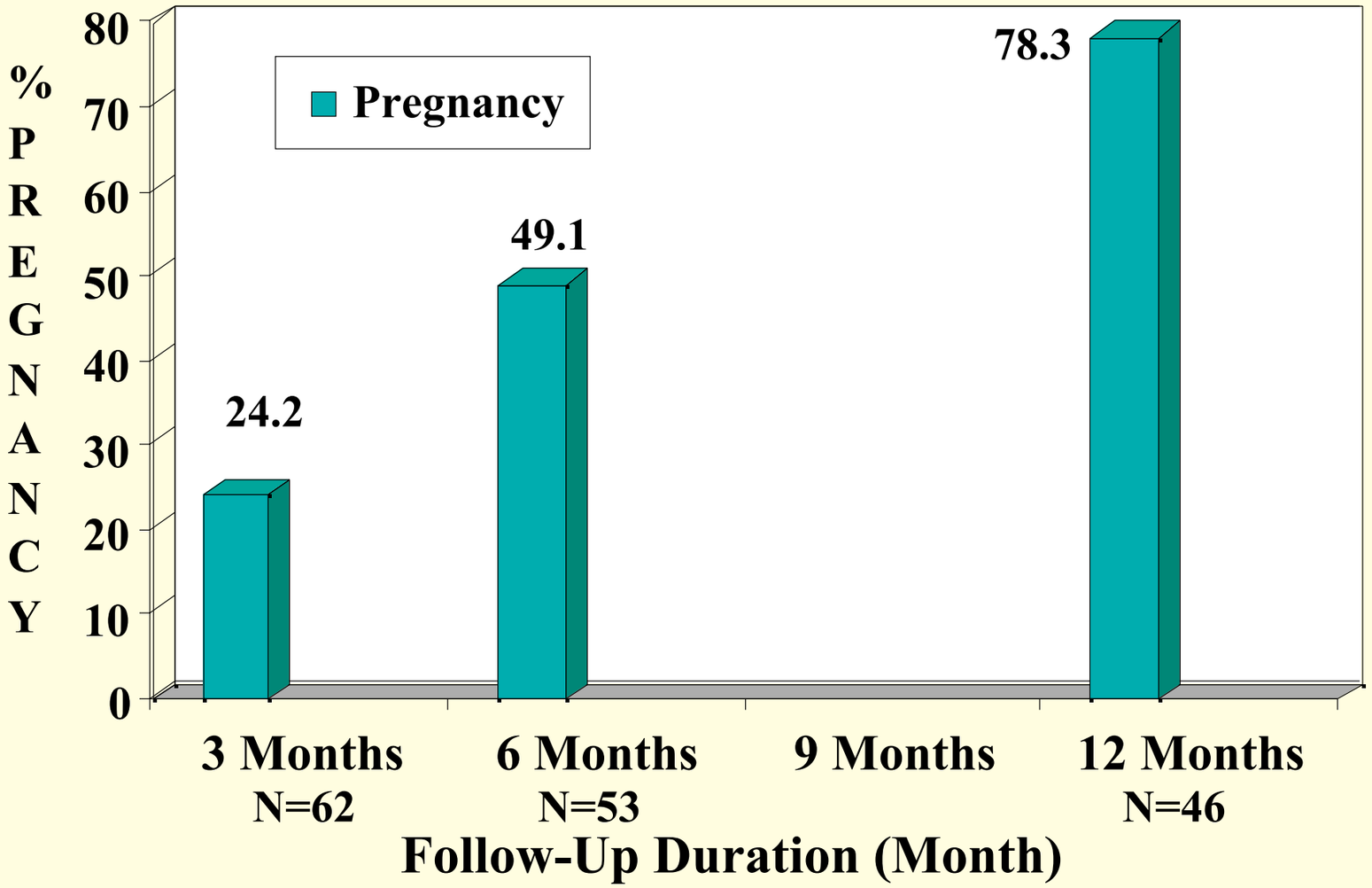
PREGNANCY OUTCOME IN INFERTILE PATIENTS



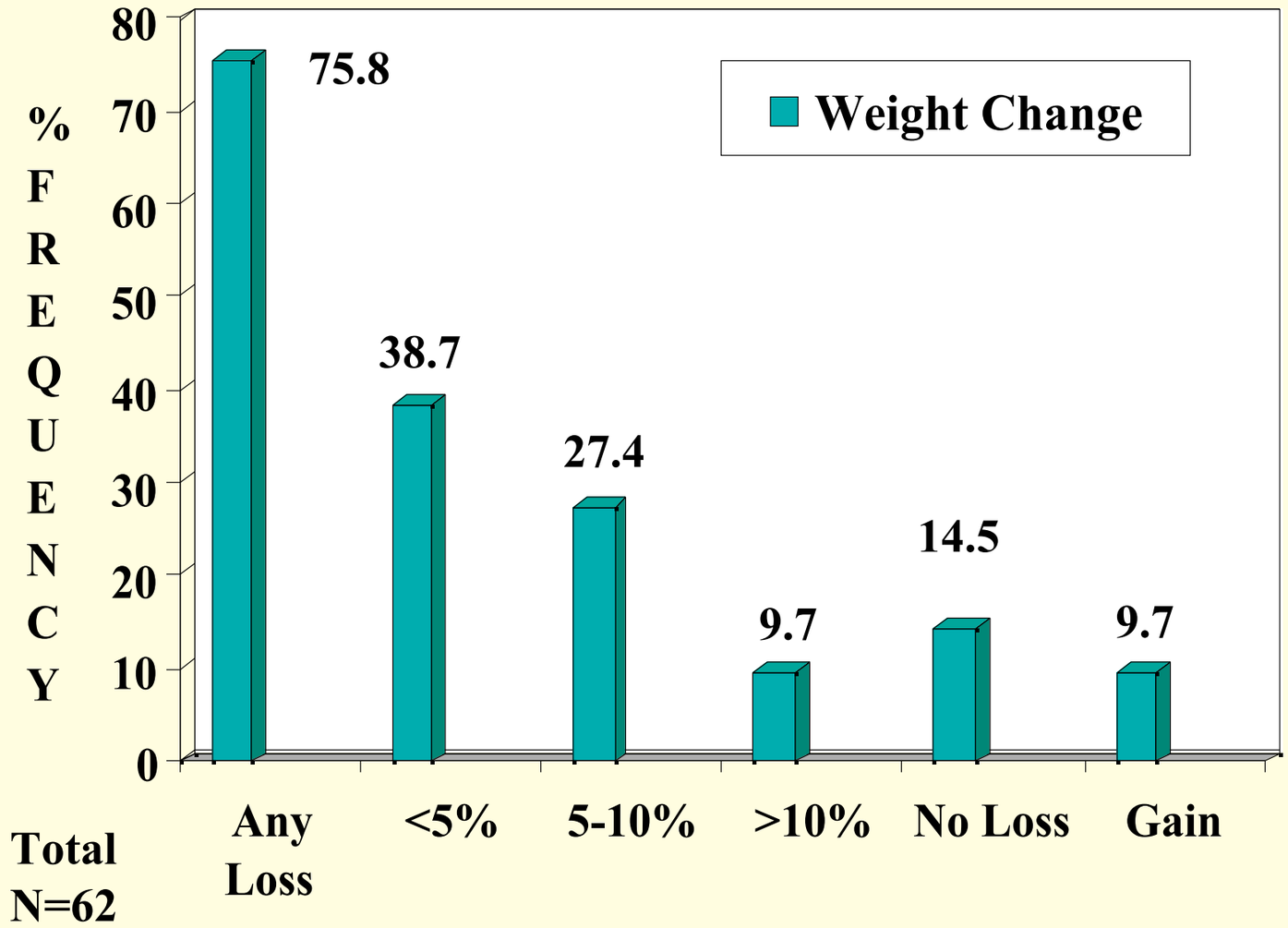
PREGNANCY OUTCOME AND INSULIN RESISTANCE



CUMLATIVE PREGNANCY RATE IN INFERTILE PATIENTS



WEIGHT LOSS DURING THERAPY



CONCLUSION

1. Metabolic disorders (IR, IGT & DM) were quite common in the obese (IR:91.8%, IGT:14.2% & DM:22.4%) and the over weight (IR:62.5%, IGT:0.0% & DM:6.3%) infertile patients

2. Normal weight infertile patients with ultrasound evidence of PCO were frequently associated with IR (55.6%) and even DM (5.6%).

3. Pregnancy (Pg) & live birth (LB) rates were higher in the non-obese group (78.3% & 94.4% respectively) than the obese group (46.2% & 83.3% respectively).

4. Patients with IR achieved successful pregnancies (Pg: 51.9%, LB: 89.3%), comparable to the non-IR patients (Pg: 100%, LB: 87.5%), following lifestyle adjustment with/without insulin sensitizing agents, plus the conventional fertility therapy & IVF.

5. Successful cumulative pregnancy rate was achieved during one year of follow-up therapy (24.2% at 3 months, 49.1% at 6 months & 78.3% at 12 months).

6. Weight loss was observed in 75.8% of patients and most of them (66.1%) lost < 10% of the original weight. Weight gain occurred in 9.7% of patients.