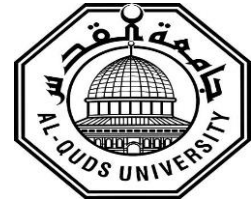


**Deanship of Graduate Studies  
Al-Quads University**



**Prevalence of Multiple Births in Selected Five Hospitals  
in West Bank: Consequences on Maternal and Neonatal  
Health**

**Sawsan Ibrahim Hassan Hamarsheh**

**M.Sc.Thesis**

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**Prevalence of Multiple Birth in Selected Five Hospitals  
in West Bank: Consequences on Maternal and Neonatal  
Health**

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## Thesis Approval

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Jerusalem-Palestine

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## **Dedication**

This thesis is dedicated to all the Palestinian women and children who deserve to have good health which promotes a healthy Palestinian society, to my parents who supported me and encouraged me all the time, to my husband, Haitham, my rock for his endless support through the years especially in times of stress, and to my kids, Mustafa, Hala, and Mohammad who are the best children a mother could hope for: happy, loving, and fun to be with.

Sawsan Ibrahim Hassan Hamarsheh

## **Declaration**

I certify that this thesis which is submitted for the degree of master, is the result of my own research, except where otherwise acknowledged, and that this study (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signed:

Sawsan Ibrahim Hassan Hamarsheh

Date: 1/6/2021

## **Acknowledgment**

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Anything is possible with faith and hope.

Sawsan Ibrahim Hassan Hamarsheh

## Abstract

The aim of this study was to determine the prevalence of multiple births, mode of conception whether spontaneous or medically assisted conception, and their consequences on maternal and neonatal health among Palestinian women in selected five hospitals in the West Bank.

This retrospective study targeted five hospitals distributed in south, middle, and north West Bank from January 2010 to December 2011. This study included data of all women who delivered more than one live born baby with gestational age  $\geq 24$  weeks. The data was obtained from the medical records department through reviewing the files of the mothers, and their newborns. A total of 912 multiple births were recorded in the medical records during the study period: 820 were twin births and 92 were triplet and quadruplet births. A total of 896 multiple births were studied: 808 were twins and 88 were triplets and quadruplets.

The findings showed that 2.2% (n=912/41,244) of all births were multiple births. Of those, 89.9% were twins, and 10.1% were triplets and quadruplets. According to the method of conception, 68.3% (n=478/700) of twins were spontaneously conceived and 31.7% (n=222/700) were conceived by medical assisted reproduction (MAR). For the higher-order multiple births (triplets and quadruplets), 83.7% (n=67/80) were conceived by MAR and 16.3% (n=13/80) were spontaneously conceived. In-vitro fertilization (IVF) and Induction of ovulation (IOO) were the methods of choice among multiple births mothers. After comparing multiple births of the two groups; spontaneous and MAR group, results showed that the women with twins and triplets in the MAR group were younger, with lower parity, higher infertility rate, and with the most usage of the cervical stitch. Women with twins in the MAR group had a higher rate of preterm delivery (61.7% vs. 51.5%) as well as cesarean delivery (78.3% vs. 52.2%). Women with triplets in the spontaneous conception group (SC) were more likely to have complications with anemia (36.4% vs. 19.6%) and hypertensive complications (18.2% vs. 5.2%). There was no maternal mortality in any of the studied groups.

Correspondingly, the medically assisted twins compared to spontaneously conceived twins had lower mean gestational age (35.4, SD 2.7 vs. 36.1, SD 2.9 weeks), and lower mean birth weight (2275.6, SD 614.7 g vs. 2402.2, SD 582.2 g) with higher incidence of neonates born premature at (<37 weeks) of gestation (61.7% vs. 51.0%), more neonates weighed <2,500 g (62.4% vs. 50.5%), more neonates were admitted to the NICU (51.5% vs. 39.6%), and had longer hospital stay, as there were more neonates with respiratory problems (35.7% vs. 26.4%), and more needed phototherapy (20.7% vs. 11.0%). Among neonates of triplets, the results indicated that both groups (spontaneous, MAR) were similar for the gestational age (32.5, SD 2.8 vs. 32.3, SD 2.6 weeks) and birth weight (1704.5, SD 426.6 g vs. 1618.9, SD 466.2 g). The incidence of respiratory disorders was higher in the MAR group (92.3% vs. 83.3%), hematologic problems were much higher (30.1% vs. 16.7%), the use of phototherapy (60.1% vs. 40.0%), and hospital stay was

longer. The mode of conception did not influence the rate of mortality among the twin and triplet groups.

The IOO-treatment had the lowest negative influence on gestational age of twin pregnancy, also it contributed to lower cesarean delivery rate, whereas it contributes to higher mortality rate among triplets. The IUI- treatment had a negative influence on the birth weight and gestational age of twins and contributed to higher hypertensive complications for mothers. The IUI-treatment contributed to higher incidence of PPROM for mothers of triplets.

In conclusion, this study suggests that twin births resulting from the use of assisted reproductive technologies are more likely to have obstetric complications and neonatal complications; however, ART had higher adverse neonatal outcomes for triplets. Our results concerning the obstetrical and neonatal outcomes after IUI treatment need further confirmation. The recommendations are to adopt policies that consider the multiple births in vital statistics assessment and to adopt strategies aimed at reducing the multiple births rates resulting from medical assisted treatments.

**Keywords:** multiple births, prevalence, maternal outcomes, neonatal outcomes

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## **List of abbreviation**

<b>Abbreviation</b>	<b>Explanation</b>
ART	Assisted reproductive technology
HOM	Higher-order multiples
IOO	Induction of ovulation
IUI	Intra uterine insemination
IVF	In vitro fertilization
MAR	Medical assisted reproduction
MOH	Ministry of Health
NICU	Neonatal intensive care unit
PCBS	Palestinian Center Bureau of Statistics
PPROM	Preterm premature rupture of membrane
SC	Spontaneous conception
SD	Standard deviation
TTTS	Twin-twin transfusion syndrome
VS	Versus
WB	West Bank
WHO	World Health Organization

## Definitions

Most of the following definitions are taken from the (Bowers, 2001 pp. 358-367) and from the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary of ART Terminology (Zegars-Hochschild et al., 2009)

**Abortion:** loss of a pregnancy before the fetus can survive outside the uterus.

**Assisted reproductive technologies (ART):** All treatments or procedures that include the in vitro handling of both human oocytes, and sperm or embryos, for the purpose of establishing a pregnancy, this includes, in vitro fertilization and embryo transfer, gamete intra fallopian transfer, zygote intra fallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surgery.

**Cervical Stitch/Cerclage:** A surgical procedure in which a purse-string type stitch in the cervix is used in an attempt to prevent premature birth.

**Chorionicity:** Term used to describe the arrangement of the chorions in a multiple pregnancy.

**Congenital anomalies:** all structural, functional, and genetic anomalies diagnosed in aborted fetuses, at birth or in the neonatal period.

**Dichorionic:** placental structure with two chorions

**Fetal death (stillbirth):** death prior to the completed expulsion or extraction from its mother of a product of fertilization, at or after 20 completed weeks of gestational age. The death is indicated by the fact that, after such separation, the fetus does not breathe or show any other evidence of life such as heart beat, umbilical cord pulsation, or definite movement of voluntary muscles.

**High-order multiple:** a pregnancy or delivery with three or more fetuses or neonates.

**Infertility (clinical definition):** a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.

**In vitro fertilization (IVF):** an ART procedure that involves extracorporeal fertilization

**Medically assisted reproduction (MAR):** reproduction brought about through ovulation induction, controlled ovarian stimulation, ovulation triggering, ART procedures, and intrauterine, intra cervical, and intra vaginal insemination with semen of husband/partner or donor.

**Monochorionic:** Refers to multiple fetuses sharing one chorion /placenta.

**Multiple gestation/ birth:** a pregnancy/delivery with more than one fetus/neonate.

**Multi fetal pregnancy reduction:** Termination of one or more fetuses in a multiple pregnancy.

**Neonatal period:** the time interval that commences at birth and ends 28 completed days after birth.

**Ovulation induction (OI):** pharmacological treatment of women with an ovulation or oligo-ovulation with the intention of inducing normal ovulatory cycles. .

**Preterm birth:** A live birth or stillbirth that takes place before 37 completed weeks of gestational age.

**Triplets:** Three babies in the same pregnancy

**Twins:** Two babies in the same pregnancy.

**Vanishing sac (s) or embryo (s):** Spontaneous disappearance of one or more gestational sacs or embryos in an ongoing pregnancy, documented by ultrasound.

## **Chapter one**

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### **Introduction**

#### **1.1 Introduction**

The natural wonder of multiple births (twins, and higher order multiples [HOM]); triplets, quadruplets and other higher order multiples) has fascinated humanity since the ancient times (Papiernik, LG. Keith, DM. Keith, & Luke, 1995, p.9). Interest in multiple births predates written history and the mythology of many races, cultures, and societies, includes stories of twins (Baldwin, 1994, p.2). With the time passing, multiple births were not regarded as a natural wonder anymore and started to be regarded as a subject of scientific research into the old question of nurture versus nature (Baldwin, 1994, p.2; Papiernik et al., 1995, p.9). The causes and health hazards of multiple births have been subject to investigation since Hippocrates's time, but this scientific interest has expanded rapidly since 1970s onwards because there was a steady rise in the rate of multiple births (Bortolus et al., 1999; Collins, 2007; Petterson, Blair, Watson, & Stanley, 1998).

Recently, multiple births became the reproductive incident that has been of great interest especially because it has been increasing more frequently, also because of the associated fetal, maternal and neonatal health problems that it entails (Qazi, 2011). Moreover, the progress in obstetric and neonatal care has created better possibilities for prevention, diagnosis and treatment of maternal, fetal and neonatal complications associated with multiple pregnancies (Olivennes, 2000).

Multiple births account for 3% of total births (Collins, 2007), whereas previously mentioned, they ranged from 0.5 to 1.0% of births (Pillitteri, 1999, p. 401). It's estimated that the twin births rate has increased by over 52% since 1980, HOM have increased even more at a rate of 400% (Collins, 2007; Barr, Poggi, & Keszler, 2003). Many reasons were associated with the increase in the rate of multiple births; review studies showed that the increase was attributed to the increase the maternal age at conception (when multiple pregnancy are more likely to occur spontaneously) and the expanded use of Medical

Assisted Reproduction (MAR), which includes ovulation induction (OI), intrauterine insemination (IUI), and assisted reproductive techniques (ART) such as in vitro fertilization (IVF) (Barr et al., 2003; Zegers-Hochschild, Admson, Mouzon, Ishihara, & Vanderopel, 2009). The increased maternal age at conception is one of the predisposing factors for conceiving multiples (Beemsterboer et al., 2006). The social shift in women's attitude to childbearing has resulted in more women choosing to delay childbearing in favor of work and career commitments (Velde, McDonald, Rindfuss, & Mills, 2011). It's estimated that the multiple births rate increased by 30% for women aged 30-40 years (Barr et al., 2003; Collins, 2007). Also, with the increase of maternal age; fertility decreases, as a result woman sometimes need to use fertility treatment to get pregnant (Bowers, 2001, p.9; Nobel et al., 2003, p.35).

However, the increased incidence of multiple births is mainly attributed to the expansion of MAR; that includes ovulation induction (OI), intrauterine insemination (IUI), and assisted reproductive techniques (ART) such as in vitro fertilization (IVF) (Zegers-Hochschild, Admson, Mouzon, Ishihara, & Vanderopel, 2009). This increases the risk of multiple births because of ovulation induction and embryo transfer (Baldwin, 1994, p.9; Grosignani, 2000).

It's reported that the incidence of multiple pregnancy associated with IVF is 27% compared with the incidence of 1% after spontaneous conception (SC) (Anbazhagan, Hunter, breathnach, Mcauliffe, & Geary, 2014). It's suggested that these techniques are responsible for about 20-30% of the increase in twin births and 30-40% in triplet births (Collins, 2007). With the availability of techniques of assisted reproduction, it's estimated that 30-50% of twins (Carrara, 2009; Hansen et al., 2009), 90% of triplets, 96% of quadruplets and 99% of quintuplets are resulted from infertility treatments (Carrara, 2009).

Medically assisted reproduction is being increasingly adopted worldwide in the treatment of infertility (Anbazhagan et al., 2014) that has increased dramatically since 1981 (Sunderam et al., 2014). According to systematic analysis of 277 demographic and reproductive health surveys (1990-2010); primary infertility affects 1.9% of women aged 20-44 years, while secondary infertility affects 10.5% of women with the same age (Mascarenhas, Flaxman, Boerma, Vandepoel, & Stevens, 2012). In the West Bank (WB), according to a survey from the Palestinian Central Bureau of Statistics (PCBS; 2013b), 8.8% of women aged 15-49 years reported infertility in 2010.

Infertile couples turned to use the infertility treatments so as to fulfill their social role as parents and to overcome the associated psychological problems of infertility (Mascarenhas et al., 2012). In the Palestinian families, infertility has a major impact on life; because the traditions and the social structure of the Palestinian society favor reproduction, making infertility a serious long-term issue (Hammoudeh, Hamayel, Abu-Remileh, & Giacaman, 2013). As a result, the infertile couples are increasingly seeking treatment since infertility treatments are becoming more available in the WB.

In the West Bank the infertile couples have the advantage of the ART and they have been able to treat infertility since 1996; when the first IVF clinic was established in Ramallah.

Since the establishment of the first clinic up till now, the awareness of means of infertility treatments has expanded. In addition to that, the accessibility to treatment has improved. In return, the demand for infertility treatments has increased which led to the increase of the number of clinics distributed all over the West Bank. With the expanded use of MAR in the WB, it's believed that this is the main cause for the increase in multiple births.

The increased incidence of multiple births is of concern; as this type of pregnancy has historically contributed to a significant proportion of maternal, fetal and neonatal complications (Barr et al., 2003), whether or not the MAR was used (Montgomery et al., 2005). Mothers of multiple births have the risk of hypertensive complications, ante and postpartum bleeding, gestational diabetes, assisted and surgical delivery, maternal anemia, premature labor and maternal mortality (Adamson & Baker, 2004). In addition to some pregnancy complications that only occur in multiple pregnancies such as intrauterine growth restriction (IUGR), Twin-twin transfusion syndrome (TTTS), and cord entanglement, taking into consideration that the above-mentioned multiple pregnancy complications are a result of sharing the placenta and the amniotic sac (Dias, Mansud-Dornan, Bhide, Papageorghiou, &Thilaganathan, 2010; Dudenhausen & Maier, 2010).

The neonates are born preterm, the mean gestational age for twins is reported to be 35 weeks and for triplets 32 weeks and quadruplets 31 weeks, with low birth weight, and they are more likely to be stillborn or experience neonatal death and have birth defects. Most of them might need to be admitted to the neonatal intensive care unit (NICU) (Adamson & Baker, 2004). In the literature, the data on whether a multiple pregnancy after medically assisted treatments increases maternal and neonatal morbidity and mortality are inconsistent; some report similar perinatal outcomes, whereas others report a higher risk of adverse perinatal outcomes, such as preterm birth, gestational diabetes, hypertension, intrauterine growth discordance, cesarean section, low birth weight, and higher NICU admissions, and others find a better perinatal outcomes after medical assisted conception (Dominguez et al., 2014)

Studies have been done worldwide to determine the incidence and to analyze the outcome of multiple births (Baxi & Kaushal, 2008). At the national level, the prevalence, and the health consequences of multiple births remain unknown. Since multiple births are becoming more visible among Palestinian families with the lack of the national studies and knowing the high-risk nature of multiple births, therefore it is increasingly important to assess such it as base for further recommendation and intervention. To get an insight about the multiple births occurrence and its health consequences in the WB, a retrospective study was carried out by the researcher to determine the prevalence of multiple births, and the proportion of multiple births according to methods of conception, and to analyze the maternal, obstetrical and neonatal outcomes in terms of morbidity and mortality in five selected hospitals in the south, center, and north of the WB in a two years period 2010-2011.

## 2.1 Problem statement

In spite of the fact that the multiple births incident is becoming more observable in the WB, the national studies regarding its prevalence, mode of conception, and the consequences on maternal and neonatal health are lacking. Few data are available about the prevalence of multiple births in the WB which is obtained from the (Palestinian Family Health Survey 2006, 2010). These surveys indicated that the proportion of women who reported that they had a history of previous multiple births is 2.9% in 2006 and 2.8% in 2010. Although this information was not available publicly until now, the researcher was able to obtain the data for the purpose of this thesis.

Medically assisted reproduction is becoming increasingly available in WB; either in the types of services or in the number of ART clinics. Surprisingly, we lack the reports that provide an in-depth picture of the ART procedures performed in these clinics and information about the indications, success rate and pregnancy outcomes of these procedures. Moreover, MAR is used today to treat different infertility etiology whereas, it was used to overcome specific types of infertility; recently it has been used for sex selection as well. One of the obstetrician's work in the field of infertility treatment reported that it's becoming observed that MAR; in particular drug stimulation is used by the couples who have a chance to get spontaneous pregnancy. Since MAR increases the risk of multiple pregnancy; the increased use of these techniques in WB with the absence of control and monitoring; will lead to increase multiple births rate, which will be a burden on the Palestinian families and the health care system.

Unfortunately, in ART, the expense and the chance of less than 50% success rate of the single cycle among patients with the best prognosis are disappointing (Adamson & Baker, 2004). On the other hand, the Palestinian Ministry of Health (MOH) can no longer support the infertility treatment as they previously did. According to data collected from the mothers, it was found that some couples preferred to conceive more than one baby rather than paying for another round of infertility treatments due to their socio-economic problems.

Despite the small percentage of multiple births 3% of all births; they are still unfavorable all over the world and considered as adverse outcomes of the MAR, because they contributed too many complications for the mother and her babies (Adamson & Baker, 2004; Baxi & Kaushal, 2008). It's well documented by research that the increased incidence of multiple births, in particular the higher-order multiple births can affect the overall complications. Multiple births account between 10 to 20% of fetal death (Montgomery et al., 2005), and 14% of infant death (Collins, 2007). Furthermore, multiple births account for 17% of all preterm births, 23% of early preterm births, 24% of low birth weight and 26% of very low birth weight (Roberts, Broomfield, & Marcucci, 2011, p.115). Although the major medical advances and the prenatal care advances improved, the outcomes of multiple births are still associated with significant medical risks and

complications for the mothers and their babies (American Society for Reproductive Medicine [ASRM], 2012).

In addition to the associated medical problems; multiple births cause psychological and economic problems, with the presence of more maternal hospitalization and loss of work due to hospitalization and home rest (Adamson & Baker, 2004). Neonatal costs increased due to a higher chance of preterm delivery and low birth weight. In addition, they are more likely to have disabilities and special needs that require ongoing pediatric care and specialist therapies which cause more pressure on families requiring neonatal and children's services.

In consideration of all the mentioned above, the presence of more families with multiple births in the WB, will be more of an economic burden for those families and the health sector. The outcomes of this type of birth will be bad in the presence of limited resources and in the absence of organizations that take care of these children. So this study aimed to determine the prevalence of multiple births in the WB, its proportion according to mode of conception and to analyze the associated maternal and neonatal morbidities and mortalities.

### **3.1 Significance of the study**

This research is considered as the first study in Palestine that aims at providing information about the prevalence of multiple births, mode of conception and maternal and neonatal health consequences. The researcher's curiosity to study multiple births is based on personal observation where multiple births occurrence is believed to be on rise and has been documented verbally by two gynecologists working in the field of infertility and has ART clinics that verified the observation and confirmed the need for further investigating of this phenomenon.

Multiple births still require special attention as they are associated with increased risks for both mother and fetus (Rizwan, Abbasi, & Muqhal, 2010). As Papiernik et al. (1995) stated that,

“The development within the field of multiple births studies serves to increase our knowledge, not only of questions concerned with the specific phenomenon of multiple births, but also of the problems it raises in terms of physiology, psychology and family or social adjustment. The study of multiple births also tends to strengthen the conviction that the defense of life and the dignity of the human race must be of a paramount concern in all scientific researches” (p. 8).

The Millennium Development Goals four and five call for the world to reduce child morbidity and mortality as well as to improve maternal health by reducing maternal mortality and morbidity especially in developing countries (Lawn, Costello, Mwansambo, & Osrin, 2007). The fact that multiple pregnancies put the mother and her babies at increased risk of complications, this study is important to identify the pattern of health consequences on women and their children where resources are not enough, and to make a comparison with other settings where there are enough resources.

In the WB there is a need to provide baseline statistics about the prevalence of multiple births, and to have awareness of the risks associated with it where the regarding data are lacking. Furthermore, this study is important to inform clinicians, researchers, the government and the community about the MAR treatment and the resulting pregnancy and birth outcomes; to provide ongoing monitoring of ART practices, success rates and perinatal outcomes.

Another reason is to provide information to the MOH, physicians and nurses with pertinent information that may help to avoid multiple gestations and to aid in patient counseling regarding the associated risks. Also, to help highlight more opportunities to aid researchers and practitioners identify areas that might require more formal, in-depth study as well as to help keep families and medical professionals up-to-date with recent trends.

#### **4.1 Goal and objectives of the study**

This retrospective study aimed to investigate the prevalence, mode of conception of multiple births whether spontaneous or medically assisted conception (IVF, IUI and IOO) and their consequences on maternal and neonatal health among Palestinian women in selected five hospitals in the WB. To achieve this goal, the following measurable objectives are set;

1. Determine the prevalence of multiple births among targeted women in the selected hospitals.
2. Identify the prevalence of multiple births as a result of spontaneous and medically assisted conception.
3. Identify the maternal and obstetrical outcomes of multiple births for both spontaneous and medically assisted conception in terms of morbidity and mortality.
4. Identify the neonatal outcomes of multiple births for both spontaneous and medically assisted conception in terms of morbidity and mortality.

#### **5.1 Research questions:**

1. What is the prevalence of multiple births among targeted women in the selected hospitals?
2. What is the prevalence of multiple births as a result of spontaneous and medically assisted conception?
3. What are the maternal and obstetrical morbidity and mortality rate of multiple births for both spontaneous and medically assisted conception?
4. What are the neonatal morbidity and mortality rate of multiple births for both spontaneous and medically assisted conception?

## **Chapter two**

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### **Literature Review**

#### **Introduction**

Literature review plays a critical role in the research to develop an evidence-based practice, inspire new research ideas, and to help lay the foundation for studies (Polite & Beck, 2006, p.133). This chapter presents previous studies related to the prevalence of multiple births, type of conception, maternal and obstetric outcomes, in addition to neonatal outcomes. Through reviewing the literature, few studies with full text were available. Therefore, we used information from the abstract of several studies because we did not have access to full text. Due to heterogeneity of the data, we described the relevant data from literature per study. A literature review for this study was undertaken using scientific resources on the internet, “Pub Med”, “MEDLINE”, and “Google”.

#### **2.1 Prevalence of multiple births**

It has been suggested that the actual rate of multiple births is probably higher during pregnancy than after birth, the loss of one of the fetuses may play a role which is considered common nowadays (Bortolus et al., 1999). Multiple births rate varies between countries and over time, it's influenced by differences in the proportion of older women giving birth, the extent of use of MAR, and the policies for preventing multiple pregnancies in those situations, as well as by other factors (Smits & Monden, 2011). Surprisingly, there are no available numbers of multiple births around the world; the only reliable national information available is in the developed countries because they have good birth registration while information for less developed regions is insufficient (Smits & Monden, 2011).

Globally, the prevalence of multiple births is estimated as 3% of all births (Collins, 2007). According to birth data in the United States, the prevalence of multiple births in 2011 was 3.5% of all births (Kulkarni et al., 2013). According to the Assisted Reproductive Technology Surveillance, multiple births constituted 3.4% of all births in 2011, of these multiple births, 3.3% were twin births, and 0.1% were higher order multiple births

(Sunderam et al., 2014). Data from the Central Bureau of Statistics in the Netherlands in 2011 showed a rate of triplets of 2 births per 1000 births (Lamb et al., 2011).

In Palestine, according to the Palestinian Family Health Survey for the years 2006 and 2010, the proportion of women reported having a history of multiple births during the study period was 3.1% in 2006 and 2010, in the West Bank the proportions were 3.0% and 2.9% in 2006 and 2010, respectively (PCBS, 2007, 2013a).

## **2.2 Prevalence of multiple births according to the method of conception (spontaneous, MAR)**

### **2.2.1. Prevalence of multiple births conceived spontaneously**

The occurrence of twins and higher order multiple births resulting from spontaneous conception has commonly been estimated by Hellin's hypothesis. This formula predicts that if the incidence of twins is (n), the incidence of triplets will be the square of (n) and quadruplets the cube of (n) and so on (Carrara et al., 2009). Her hypothesis appeared again in Fellman and Erisksson's study, where twins can occur once in every 80 births, triplets once in every 8100 births, and the quadruplets once in every 729,000 births. But it has been proven mathematically that Hellin's law doesn't hold as a general rule because it is concerned with theoretical rates which showed discrepancies (Fellman & Eriksson, 2009).

The incidence of twin births resulted from spontaneous conception varies worldwide, from low incidence of 2-9 per 1000 births in whole eastern, south-eastern and southern Asia, to the intermediated incidence of 9-20 per 1000 births in North Africa, American, Asia, Oceania, and Europe, to the highest incidence in African countries especially Nigeria, Seychelles, Transvaal and Zimbabwe of more than 20 per 1000 deliveries (Hoekstra et al., 2008).

In Switzerland, a retrospective study was done to determine the incidence of higher-order multiple births from 2005 to 2008 and its evolution over the last twenty years. It showed that there were 91 triplets and 2 quadruplets, 27.4% of triplets occurred spontaneously, while the two sets of quadruplets resulted from medically assisted conception (Mieth, Erfeld, Douchet, Wellmann, & Bucher, 2011).

In Arab countries, data from a survey from 76 developing countries (low- and middle-income countries) showed that the twinning rate after spontaneous conception was 17.7 per 1000 births in Egypt and 14.4 per 1000 births in Jordan (Smits & Mendon, 2011).

Literature lacked for the prevalence of triplet and quadruplet pregnancies or births after spontaneous conception. According to a survey conducted by (Smits & Mendon, 2011), the birth rate of triplets was 285 per million births in the big twinning countries of Africa, 155 per million births in other African countries, 68 per million births in south and south-east Asia and 83 per million births in Latin America excluding the Caribbean. The number of quadruplets in this survey was 12, which was insufficient to draw any meaningful conclusion in this study.

### **2.2.2. Prevalence of multiple births conceived by medical assisted reproduction**

As stated by Dominguez et al. (2014), around 22% of all deliveries after ART occur in pregnancies with more than one fetus. For the non-ART treatments (including fertility drugs that are used with timed intercourse or intrauterine insemination), it's estimated that up to 30% of gonadotropin stimulated pregnancies are multiples, most of these pregnancies are twins, and up to 5% are triplets or more (ASRM, 2012).

According to birth data in the United States, 36% of twin births and 77% of triplet and higher-order births were attributed to MAR in 2011 (Kulkarni et al., 2013). According to the Assisted Reproductive Technology Surveillance, 19.8% of total multiple births was after ART in 2011. The surveillance also indicated that of all of the twin births; 19.3% were after ART and of all higher-order multiple pregnancies; 32.2% were due to ART conception (Sunderam et al., 2014). In Canada, 29.1% of twin pregnancies and 0.9% of triplet and higher-order pregnancies occurred following the use of ART in 2009 (V. Shah, Alwassia, K. Shah, Yoon, & P. Shah, 2011). In Switzerland, 48.4% of triplet births resulted from IVF or Intra cytoplasmic sperm injection (ICSI), and one quadruplet birth resulted from IVF (Mieth et al., 2011).

Data on prevalence of multiple births resulting from IOO and IUI are very limited. According to birth data in the United States, 19% of twins and 45% of the higher-order multiple births were attributable to non-IVF fertility treatments in 2011 (Kulkarni et al., 2013). In Switzerland, 24.2% of triplet births occurred after ovulation induction, and among two sets of quadruplets, one of them resulted from ovulation induction (Mieth et al., 2011).

## **2.3 Maternal and obstetric outcomes of multiple births according to the method of conception (spontaneous, MAR).**

The focus of most of the studies that investigated the maternal and obstetric outcomes of multiple births was on the outcomes of twin pregnancies, whereas similar studies for the higher order multiple births have been very limited. On the other hand, most of the studies that investigated the maternal and obstetric outcomes according to conception methods concentrated on ART (leaving out ovulation induction and IUI).

### **2.3.1. Maternal and obstetric outcomes of twins according to the method of conception (spontaneous, MAR)**

In Portugal, Dominguez et al. (2014) compared the obstetric outcomes of 180 induced twins (41% IVF, 27% ICSI, and 31.5% OI) with 698 spontaneously conceived twins in the period between January, 1996 and December, 2011. The analysis revealed that the women in the induced group were older, had higher rates of infertility (92.2% vs. 1.7%), and most were nulliparous (88.3% vs. 49.9%). There was no significant difference between groups in terms of maternal medical histories including (hypertensive, endocrine, renal, or other systemic disease) or bad habits such as (tobacco, alcohol and drugs use).

Dominguez et al. further indicated that the induced group had higher incidence of first trimester bleeding (12.2% vs. 6.0%), gestational diabetes (8.3% vs. 4.4%) and intrauterine discordant growth (11.1% vs. 4.3%) in comparison with the spontaneous group. The incidence of preterm premature rupture of the membrane (PPROM) was less frequent in the induced group (12.8% vs. 23.9%), as well as the preterm delivery at gestational age  $\leq 32$  weeks (14.0% vs. 22.5%), and at  $< 35$  weeks (32.4% vs. 40.5%). There was no significant difference between groups in terms of anemia (3.9% of spontaneous group vs. 5.0% of induced group), infections (7.6% vs. 8.9%, respectively), pregnancy- induced hypertension (PIH) (3.7% vs. 3.3%, respectively), Preeclampsia (4.6% vs. 3.3%, respectively), HELLP syndrome (0.9% vs. 0.6%, respectively), fetal malformation (1.6% vs. 1.7%, respectively), intrauterine fetal death (IUFD) (2.4% vs. 3.3%, respectively), twin-to-twin transfusion syndrome (TTTS) (2.1% vs. 1.1%, respectively), and intrauterine growth restriction (IUGR) (12.8% vs. 13.9%, respectively). The induced group had higher cesarean section rates (63.9% vs. 50.6%). No difference between groups was found in the puerperium complications (18.9% of spontaneous group vs. 20.5% of induced group).

The study also showed that there was no effect for the type of MAR (IVF, OI, and ICSI) on pregnancy outcomes, the only difference was found in maternal age, where the women in the OI group were younger; the percentage of women  $< 35$  years old was (12.5% of OI, 6.8% of IVF, 2.0% of the ICSI). In this study, the majority of women were nulliparous (85.7% of OI, 86.3% of IVF and 95.9% of ICSI group), and had higher rates of infertility (85% vs. 95.9%, 93.9%, respectively). There was no difference in the incidence of medical history (hypertension, endocrine, renal, or other systemic). The recorded complications of all groups were 1<sup>st</sup> trimester bleeding (8.9% of the OI, 13.7% of the IVF, and 12.2% of the ICSI), anemia (3.6% vs. 4.1% vs. 6.1, respectively), infections (7.1% vs. 11%, vs. 8.2%, respectively), PIH (1.8% vs. 2.7% vs. 6.1%, respectively), preeclampsia (3.6% vs. 1.4% vs. 6.1%, respectively), gestational diabetes mellitus (GDM) (7.1% vs. 8.2% vs. 10.2%, respectively), PPRM (16.1% vs. 13.9% vs. 6.1%, respectively), preterm delivery  $\leq 32$  wks. (10.7% vs. 16.7% vs. 14.3%, respectively), and HELLP syndrome (2%) of the ICSI group, no cases were present in IVF and OI groups. Cesarean delivery was performed for (57.2% of the OI, 67.1% of the IVF, and 67.3% the ICSI), without any significant difference. Lower incidence of Puerperium complications was observed in OI group (9.3% of the OI vs. 27.8% of the IVF vs. 20.8% of the ICSI) (Dominguez et al., 2014).

Moreover, Dominguez et al. analyzed the fetal data according to the mode of conception, and showed no statistical difference between groups in terms of IUGR (17.9% of the OI, 13.7% of the IVF, 10.2% of the ICSI group), growth discordance 20% (12.5% vs. 8.2% vs. 14.3%, respectively), and the admission to NICU 1<sup>st</sup> and, or 2<sup>nd</sup> twin was required for (54.8% of the IVF vs. 38.5% of the OI vs. 38.1% of ICSI). Intrauterine fetal death was found in OI and IVF group (1.8% vs. 6.8%, respectively). Fetal malformation was found in the OI and ICSI groups (1.8% of OI vs. 4.1% of ICSI), same as TTTS (1.8% of OI vs. 2% of ICSI).

In the United Kingdom, the maternal and perinatal outcomes of twin pregnancies (conceived spontaneously and by medically assisted conception) were studied through a

prospective observational study between (May 2007 and October 2009). In this study 76% of twins were conceived spontaneously while 24% were conceived artificially (0.2% by IUI, 2.3% by ICSI, 4.1% by OI and 17.2% by IVF). The analysis of obstetric outcomes revealed no significant difference in the outcomes of twins conceived spontaneously or by medically assisted conception. The study showed that the women who used the MAR were older than those conceived spontaneously (mean age 35.4 vs. 31.9 yrs), and of a lower parity (29% had  $\geq 1$  birth vs. 58%), smoked more (15% vs. 4%) and had higher body mass index. There was no association in the maternal medical history and mode of conception (Anbazhagan et al., 2014).

Anabazhagan et al. further investigated the obstetrical complications, no significant difference was found in terms of hypertensive complications (PIH and preeclampsia) (9% of spontaneous group vs. 11% of medically assisted conception group), GDM (1.4% vs. 3%, respectively), PPRM (3% vs. 2%, respectively), placental abruption (<1% vs. 1%, respectively), antepartum hemorrhage (APH) (unclassified) (5% vs. 10%, respectively), placenta previa (1% vs. 2%, respectively), obstetric cholestasis (1% vs. 3%, respectively), and preterm delivery (18% vs. 15%, respectively). TTTS occurred in 3% of women who conceived spontaneously and it was not found in the medically assisted group.

In a retrospective study in Germany held by (Bamberg et al., 2012) to compare the maternal characteristics and pregnancy outcomes of twin pregnancies spontaneously conceived and after fertility treatment (FT) in the period between January, 1998 and October, 2008), the prevalence of twins was 3.3% of all births, 65.6% resulted from spontaneous conception, while 34.4% resulted from medical assisted conception (6.3 by IUI, 18.6% by OI, 33.3% by IVF, and 41.8% by ICSI). Study findings also showed a higher maternal age in the FT group (mean, 32.5 yrs. in FT vs. 30.1 yrs. in the spontaneous group). The women in the spontaneous group were shorter (mean 166.62 cm, vs. 167.43 cm). There was no difference between groups in terms of maternal body mass index and maternal weight.

Bamberg et al. also indicated higher incidence of obstetrical complications in pregnancies resulted from fertility treatments in terms of dichorionic twin prematurity (mean gestational age 34.2, SD 3.6 weeks in FT group vs. 35.1, SD 3.0 weeks in SC group), APH(7.7% vs. 3.4%), cervical insufficiency (17.6% vs. 10.0%), PROM (2.3% vs. 0.6%), amniotic membrane prolapsed (2.3% vs. 0.6%), postpartum hemorrhage (9.9% vs. 6.0%), anemia at puerperium (43.4% vs. 37.0%) and hypothyroidism (4.5% vs. 1.5%). There were no significant differences between groups with regards to preeclampsia (3.0% of SC group vs. 3.3% of the FT group), HELLP syndrome (0.9% vs. 1.4%, respectively), GDM (3.2% vs. 4.5%, respectively), and PIH (1.8% vs. 2.3%, respectively). The incidence of cesarean section was higher in the FT group (72.3% vs. 63.9%). There was no significant difference in the frequency of combined mode of delivery (the first twin was born vaginally, the second by a cesarean) (2.3% in SC group vs. 1.7% in FT group).

A retrospective study was done by (Huang et al., 2006) to compare the maternal and neonatal outcomes of the twin births conceived by IVF (n=81), and IUI (n=63) with those

conceived spontaneously (n=50). There was no significant difference between study groups in terms of the mean maternal age at delivery (31.8, SD 3.7 for spontaneous vs. 32.1, SD 3.0 years for IUI vs. 33.7, SD 4.6 years for IVF/ICSI), the incidence of preterm delivery <37 weeks (40% of spontaneous vs. 36.5% of the IUI vs. 43.2% of the IVF/ICSI groups) and the incidence of postpartum hemorrhage (18% of the spontaneous vs. 14.3% of the IUI vs. 9.9% of the IVF/ICSI groups). Moreover, the incidence of preterm labor was (30.0% of spontaneous vs. 25.5% of IUI vs. 32.1% of IVF/ICSI group), PIH was (8.0% of spontaneous vs. 7.9% of IUI vs. 12.3% of IVF/ICSI groups), and GDM was (4.0% of spontaneous vs. 0.0% of IUI vs. 6.2% of IVF/ICSI groups) was similar among the three groups. The incidence of the PROM was found lower in the IUI group (3.2% of the IUI vs. 18% of the spontaneous vs. 13.6% of the IVF/ICSI group). Rate of Cesarean delivery was higher in IUI and IVF/ICSI groups (95.1% of the IVF/ICSI vs. 90.5% of the IUI vs. 74% of the spontaneous group). In this study, abruptio placenta was found only in the IUI group (1.6%), placenta accreta was found in IVF/ICSI groups (1.2%), while placenta previa was found in the IVF and the IUI groups (4.9% vs. 6.3%, respectively).

In Taiwan, Chi-Hong Ho et al. (2005) conducted a study to determine whether twin pregnancies resulting from medically assisted conception are at an increased risk of obstetrical and perinatal complications. They compared the obstetric outcome of 54 twins conceived spontaneously, 31 by ovulation induction, and 74 by IVF. The study results showed that the mothers in the medically assisted conception group were more likely to be older than mothers in the spontaneous group (mean 33.1 years in the ART vs. 32.2 years in the OI vs. 29.9 years in the spontaneous group). Most cases were nulliparous (78.7% in ART vs. 77.4% in OI vs. 66.7% in spontaneous group), the difference was not significant. Previous miscarriage was lower in the spontaneous group (3.7% in spontaneous vs. 14.9% in ART vs. 19.4% in OI).

Chi-Hong Ho et al. further showed in their study that the mean gestational age at delivery was comparable among the three groups (35.8 in ART vs. 36.6 in OI vs. 35.2 weeks in SC). In addition, the incidences of hypertensive disorders were (8.1% in ART vs. 9.7% in OI vs. 3.7% in the spontaneous group), PPRM (14.9% vs. 12.9% vs. 22.2%, respectively), preterm contractions (28.4% vs. 38.7% vs. 38.9%, respectively), preterm admission (39.2% vs. 35.5% vs. 48.1%, respectively), cesarean delivery (79.3% vs. 96.8% vs. 92.6%, respectively) and discordant birth weight (21.6% vs. 22.6% vs. 25.9%, respectively). Antepartum hemorrhage was found in the ART and OI groups (5.4% in ART vs. 12.9% in OI), without significant difference, same as for the placenta previa (1.4% vs. 3.2%, respectively). Preterm delivery <34 weeks was significantly higher in the ART group than in the OI group (18.9% in ART vs. 3.2% in OI vs. 29.6% in SC). Fetal reduction was performed for (17.6% in the ART vs. 16.1% in the OI).

In New York, a retrospective study conducted by (Narine et al., 2003) to compare the perinatal outcomes of twins conceived by medical assisted reproduction (IVF, IUI, and OI) or natural conception. Abstract data showed that the twin pairs that resulted after the medically assisted conception were delivered for older mothers (4 years older than spontaneous conception), with earlier gestational age (2.2 weeks earlier than spontaneous

conception twins), and most frequently by cesarean section. The difference was also found in the birth weight of twin A and B in study groups, which was lower in the medically assisted conceived twin A and B. There was no difference in the incidence of birth weight discordance in either group.

A study conducted by Putterman, Figureoa, Garry, and Maulik (2003) to compare the live born twin pregnancies conceived after IVF or OI with spontaneously conceived twin pregnancies. Abstract data showed that the women in the IVF group were older and primiparous. Bad obstetric history found in women in the OI group. There was no difference in the gestational age at delivery, antepartum complications, and mode of delivery. The researchers also found that the number of infants with low birth weight (LBW) was lower in the IVF group than it was in the spontaneous group, while there were similar neonatal outcomes among both groups.

In France, Olivennes et al. (1996) compared perinatal outcomes of 72 twin pregnancies conceived after IVF, 82 after OI, and 164 after spontaneous conceptions. Abstract data showed that the women in the IVF group were older and of higher socioeconomic class. There were no differences between groups in this study's main outcome measures (hypertension, PROM, threatened premature labor, low birth weight, prematurity with the exception to the rate of emergency cesarean sections). Preterm birth was found in (38.9% of the IVF vs. 45.1% of the OI vs. 39.6% of the spontaneous conception group). Small for Gestational Age was also found in (18% of the IVF vs. 23.2% of the OI vs. 22.7% of the spontaneous conception group). The perinatal mortality rate was (3.47% of the IVF vs. 3.05% of the OI vs. 4.27% of the spontaneous conception groups).

In Arab countries, a study in Lebanon was performed to compare maternal and neonatal outcomes of twins resulting from spontaneous and IVF conception. Abstract data showed lower gestational age in the IVF group (mean 35, SD 3 weeks vs. 36, SD 3 weeks), with higher incidence of preterm labor and delivery (67.9% vs. 41.1%) and operative delivery (76.8% vs. 58.0%). With regards to pregnancy complications, there was no difference in the frequency of PIH, GDM, placenta previa, and PPRM (Nassar et al., 2003).

In Israel, Adler-leavy, Lunenfeld, and Leavy (2007) carried out a study to compare the obstetrical characteristics in 558 IVF twin delivery and 478 twin delivery conceived by ovulation induction with 3694 twin deliveries conceived spontaneously. Abstract data showed that after controlling the maternal age and nulliparity, the women who conceived with the assistance of IVF and OI had significantly higher risk for GDM, and cesarean section. While, in the IVF conceived pregnancies the gestational age at birth was lower.

A retrospective study in the United Arab Emirates was conducted to compare obstetric and perinatal outcomes of twin pregnancies after medically assisted and spontaneous conception. Abstract data showed that the mothers in the ART group who were older and nulliparous, were more likely to deliver by elective cesarean section. There was no statistically significant difference in the incidence of preterm delivery, mean gestational age at delivery and birth weight. In addition, there was no significant difference between groups in the neonatal complications (Zaib-un-Nisa, Ghazal-Aswad, & Badrinath, 2003).

In Israel, Daniel et al. (2000) reviewed the perinatal outcomes of 121 twin pregnancies conceived spontaneously, 72 twins conceived by OI and 193 twins conceived by ART. The study demonstrated that the ART group had higher mean maternal age (32, SD 4.8 in ART vs. 29, SD 4.7 in OI group vs. 30.7, SD 5.0 years in the spontaneous conception group), and more nulliparous women (77.7% vs. 65.5% vs. 32.2%, respectively). In addition, the ART conceived pregnancies had lower gestational age at birth (mean 35.4, SD 2.5 in ART vs. 36.8, SD 2.2 in OI vs. 36.2, SD 3 in the spontaneous conception group), and higher preterm delivery <34 weeks (25.0% vs. 9.7% vs. 20.7%, respectively). With regards to pregnancy complications the analysis revealed higher incidence of PIH in the ART group (18.3% of the ART, 8.3% of the OI, 9.9% of the spontaneous), same as premature uterine contraction (36.5% vs. 30.6% vs. 22%, respectively), uterine bleeding (10.6% vs. 1.45 vs. 4.1%, respectively), IUGR (7.7% vs. 2.8% vs. 2.5%, respectively), growth discordance (17.2% vs. 6.9% vs. 7.5%, respectively), IUFD (5.1% vs. 1.4% vs. 0.9%, respectively) and cesarean section (43.4% vs. 33.3% vs. 33.6%, respectively). Similar results were found in the incidence of the GDM (4.8% of the ART vs. 7% of the OI vs. 4% of the spontaneous group), and in the distribution of the vertex and non-vertex presentation. The incidence of peripartum bleeding, fever and the mean duration of hospitalization were also comparable among the groups. In this study, fetal reduction was performed for (22.3% of the ART vs. 6.9% of the OI group).

### **2.3.2. Maternal and obstetric outcomes of triplets and quadruplets according to the method of conception (spontaneous, MAR)**

Studies comparing the outcomes of triplets and quadruplets conceived spontaneously with others conceived by using MAR are scarce and revealed inconclusive results. In Abakaliki, southeast Nigeria (Umero, Aneziokoro, & Egwuatu, 2011) reviewed the maternal data on spontaneously conceived higher-order multiples (21 sets of triplets and one set of quadruplets). In this study, the higher-order multiple births consisted of 0.13% of all deliveries and 4.0% of all multiple births, and triplet births consisted of 0.12% of all births. The mean maternal age of triplets was (mean 28, SD 7.2 years; range 23-34 years), with higher parity (3 or more). The pregnancy complications included, PPRM (23.8%), preterm labor (95.2%), and other complications (anemia 28.6%, hypertensive complications (PIH and preeclampsia) 9.3%, urinary tract infection 9.5%, APH 9.5%, and postpartum hemorrhage which was present in one case). The majority of triplet pregnancies (19 sets) were delivered vaginally, whereas 2 sets were delivered by cesarean section. In the same study, one set of quadruplets was also evaluated and it was found that the woman's age was 30 years old, a housewife, with 2 previous births. This set was delivered by cesarean section at 32 weeks of gestation.

A retrospective cohort study was conducted by Fennessy et al. (2015) to evaluate all triplet pregnancies (53 pregnancies) according to mode of conception (spontaneous vs. ART pregnancies) between 1999 and 2011. Twenty-five pregnancies following ART treatments (25 sets following OI and 8 following IVF) and 28 sets conceived spontaneously were evaluated for this study. There was no significant difference in the mean mothers' age for

both groups (32.9, SD 3.7 years for the ART group vs. 31.6, SD 4.6 years for the spontaneous group). The majority of the mothers in both groups had no previous medical diseases, with the exception of polycystic ovarian syndrome which reported for 5 mothers (20%) only in the ART group. Cervical stitch was applied for one mother (4%) in the ART group and for one mother (4%) in the spontaneous group.

Fennessy et al. further analyzed the pregnancy complications and found no significant difference between the study groups in the incidence of preterm labor (28% in ART vs. 36% in the spontaneous group), PIH (24% vs. 14%, respectively), PPRM (16% vs. 21% respectively), GDM (8% vs. 11%, respectively), preeclampsia (12% vs. 7% respectively), placental abruption (4% of the ART vs. 4% of the spontaneous group), chorioamnionitis (4% vs. 7%, respectively), TTTS (8% vs. 18%, respectively), and fetal death (7% vs. 5%, respectively). The majority of cases in both groups (89% of the ART vs. 88% of the spontaneous) were delivered by cesarean section without any significant difference. Of all cases delivered by cesarean section in both groups, the majority had emergency cesarean section (72% in the ART vs. 61% in the spontaneous), most commonly for fetal distress, among which was being in preterm labor. Elective cesarean section was performed for (16% in the ART vs. 29% in the spontaneous). In this study, vaginal delivery has been performed for (12% mothers in the ART and 11% in the spontaneous group) without any significant difference.

In Israel, Lipitiz et al. (1993) conducted a prospective clinical study to compare the effect of fertility drugs and IVF on the outcomes of triplet pregnancies between 1984 and 1992. Among 106 triplet pregnancies, 81 triplet pregnancies that progressed beyond 25 weeks were included in this study, among these, 6 triplet pregnancies were a result of spontaneous conception, 57 were a result of ovulation induction, and 18 were a result of IVF conception. Abstract data showed that the mean gestational age and birth weight were similar in the study groups. There was no significant difference between groups in the incidence of stillbirth. Moreover, the frequency of premature contractions, PPRM, cesarean section was similar in the ovulation induction and IVF pregnancies.

Fitzsimons, Bebbington, and Fluker (1998) conducted a study to investigate if the ART multiple births have better outcomes than those resulting from spontaneous conception. An investigation took place for 16 triples who were conceived by ART and 16 triples who were conceived spontaneously. The abstract data showed that after matching for maternal age, parity, fetal number, and the presence of maternal medical problems the incidence of cerclage and number of antenatal visits were higher in triplets resulting from medically assisted conception. Perinatal outcomes in terms of (mean gestational age, birth weight, rate of preterm labor, PROM, PIH, GDM and neonatal morbidity were not significantly different between the groups. Furthermore, there was no difference between groups in terms of mortality rate.

In Portland, Bley and Collins (1990) reviewed the epidemiology, management and outcome of 71 quadruplet pregnancies. The majority of these pregnancies, 67 (94%) followed ovulation induction therapy. Abstract data showed that the mean gestational age

was 31.4 weeks, and the mean birth weight was 1,482 grams, where 14% of these women had cervical stitches. The most common complications during pregnancy that were found were; first-trimester bleeding (35%), toxemia (32%) and anemia (25%) in addition to premature labor. Out of these cases 89% were delivered by cesarean section. The rate of stillbirth was 29 per 1000, perinatal mortality rate was 37 per 1000 and neonatal mortality was reported for 67 per 1000.

## **2.4 Neonatal outcomes of multiple births according to the method of conception (spontaneous, MAR)**

Few studies were also available that investigated the neonatal outcomes of multiple births according to method of conception in general and for triplets and quadruplets in particular. On the other hand, for most of the studies that compared the neonatal outcomes according to mode of conception, only ART was evaluated.

### **2.4.1. Neonatal outcomes of twins according to method of conception (spontaneous, MAR)**

Anbazhagan et al. (2014) studied the perinatal outcomes of 1504 twins resulting from spontaneous pregnancy and 466 twins resulted from medically assisted conception between May, 2007 and October, 2009. There was no significant difference in the outcomes of twins in both groups even after adjustment for chorionicity, maternal age, parity, gestational age at delivery, and smoking status in terms of median gestational age (37 weeks for both groups), median birth weight (2,520 g for spontaneous group vs. 2,538 g for medical assisted conception group), percentage of weight discordance (9% vs. 10% respectively), severe discordance >20% (22% vs. 24% respectively). In addition, there was no significant difference in the incidence of neonatal intensive care unit (NICU) admission (44% of twins in both groups), and length of stay (median 8; range 1-21 days) for the spontaneous group compared to (median 7; range 0-18 days) for the medical assisted conception group, hypoxic ischemic encephalopathy (HIE) (0.1% vs. 0.2% respectively), peri ventricular leukomalacia (PVL) (0.2% vs. 0.6% respectively), necrotizing enterocolitis (NEC) (1% of the newborns of both groups), respiratory distress syndrome (RDS) (14% vs. 13%, respectively), and sepsis (6% vs. 4%, respectively). Perinatal death reported in 13 per 1000 (20/1504; 1%) in the spontaneous group and 6 per 1000 (3/466; 0.6%) in the medical assisted conception group, without any significant difference. Furthermore, there was no significant difference between the groups in the terms of the percentage of composite complications (death, HIE, PVL, NEC, RDS or sepsis).

Huang et al. (2006) compared the neonatal morbidities between the spontaneous, IUI and IVF/ICSI groups; and they found insignificant differences between the groups. The mean gestational age among those groups was (36.0, SD 2.3 for the IVF vs. 36.2, SD 2.4 for the IUI vs. 36.4, SD 2.8 weeks for spontaneous group). The mean birth weight was (2,407, SD 40 for IVF vs. 2,359, SD 46 for IUI vs. 2,434, SD 58 g for spontaneous group). Low birth

weight was found in (37.0% of the spontaneous vs. 46.0% of the IUI vs. 48.0% of the IVF/ICSI group). Very low birth weight was found in (7.0% of the spontaneous vs. 6.3% of the IUI vs. 5.6% of the IVF/ICSI group). The other neonatal outcomes resulted were; mild depression (11.0% of the spontaneous vs. 9.5% of the IUI vs. 11.1% of the IVF/ICSI group), severe depression (1.0% vs. 1.6% vs. 3.7%, respectively), stillbirth (5.0% vs. 2.4% vs. 1.2%, respectively), neonatal morbidity was found in (13.0% vs. 15.9% vs. 19.8%, respectively) and the neonatal mortality was found in (3.0% vs. 0.8% vs. 0.6%, respectively).

Chi-Hong Ho et al. (2005) investigated the perinatal and neonatal outcomes in 74 IVF twin pregnancies, 31 OI pregnancies, and 54 spontaneous pregnancies according to birth order of twins (first and second twin). The analysis revealed that the results were comparable in terms of the mean birth weight of the first and the second twin (2,330/2,208 g in ART, 2,396/2,355 g in OI group, 2,247/2,076 g in spontaneous group), ratio of male gender (52.7%/51.4% of the ART vs. 61.3%/67.7% of the OI vs. 59.3%/51.9% of the spontaneous group), the incidence of small for gestational age (23.3% /33.3% of the ART vs. 33.3% /41.9% of the OI vs. 24.5% /42.3% of the spontaneous group), and stillbirth (0/1.4% of the ART vs. 3.2%/0 of the OI vs. 1.9/3.7% of the spontaneous group). Apgar score (<7) at 1 and 5 minutes was reported for the first twin of the spontaneous group in comparison with the ART group (39.6%/5.1% of the spontaneous vs. 17.6%/1.4% of the ART group).

Furthermore, Chi-Hong Ho et al. found that the newborns in the spontaneous group were at a higher risk of having hypoglycemia (15.2% of the spontaneous vs. 13.1% of the OI vs. 5.4% of the ART group), congenital anomalies (20.0% of the spontaneous vs. 3.3% of the OI vs. 3.4% of the ART group), RDS needing ventilation (13.3% of the spontaneous vs. 3.3% of the OI vs. 2.7% of the ART group), and perinatal death (9.3% of the spontaneous vs. 3.2% of the OI vs. 2.7% of the ART group). Duration of NICU admission was also higher in the spontaneous group (mean 42.5, SD 50.4 for spontaneous vs. 17.1, SD 29.5 for OI vs. 19.1, SD 21.4 days for ART group). The incidence of NICU admission was comparable between groups (23.1% of the ART vs. 18.0% of the OI vs. 31.4% of the spontaneous group), as well as anemia (2.7% vs. 1.6% vs. 6.7%, respectively), jaundice (22.4% vs. 18.0% vs. 28.6%, respectively), respiratory disorder not requiring ventilation (21.1% vs. 13.1% vs. 17.1%, respectively), and infectious disorders (4.1% vs. 3.3% vs. 6.7%, respectively), in addition to other complications (gastrointestinal bleeding, gastro esophageal reflux, and pericardial effusion) (4.8% of the ART vs. 1.6% of the OI vs. 3.8% of the spontaneous group). Retinopathy of prematurity was found in the ART and the spontaneous group (2.0% of the ART vs. 5.7% of the spontaneous group), without any significant difference.

The abstract data of Zuppa, Marahlano, Scapillati, Crescimbin, and Tortola (2001) study showed that the incidence of the neonatal outcomes including the incidence of premature birth, and lower gestational age were higher in the medically assisted twin pregnancies than that resulting from spontaneous conception. Also, the twins resulting from medically assisted conception had higher incidence of respiratory diseases and severe depression at

birth than the spontaneous conception group, despite similar gestational age and birth weight.

In Arab countries, namely Lebanon, the abstract data from (Nassar et al., 2003) study showed lower birth weight of twin A and twin B resulted from IVF conception (on the average, 230 gram lighter), higher incidence of RDS, NICU admission, and a need for mechanical ventilation and pneumothorax. However, IUGR was more frequent in twins after spontaneous conception (36.6% spontaneous conception vs. 25.0% IVF).

In Israel, Daniel et al. (2000) analyzed the perinatal outcomes of twin births according to the birth order (twin A and B). Among the three groups (spontaneous, ART, and OI), the ART group had a higher incidence of male gender for the first twin, whereas this incidence was high in the second twin for the other groups. In addition, the mean birth weight for the 1<sup>st</sup> and the 2<sup>nd</sup> twin in the ART group was lower than the mean in the other groups (2,271, SD 537/ 2,126, SD 547 for the ART, 2,392, SD 539/ 2,427, SD 503 for OI, and 2,429, SD 639/ 2,356, SD 592g for spontaneous group), with the presence of more infants who weighed <1,500 g and fewer infants who weighed >2,500 g specifically the second twin. Furthermore, in the ART group, the incidence of Apgar score (<7) at 5 minutes for the first twin, was higher than the incidence in the other groups, and there were more neonates for both the first and the second twin that required admission to the NICU.

Daniel et al. further showed that the incidence of Apgar score <7 at 1 min for the first and the second twin was not significantly different between groups (9.8%/ 9.2% for ART vs. 4.2% /8.7% for OI vs. 5.9% /9.5% for spontaneous conception group), as well as the incidence of anemia (2.1% /0 for ART vs. 1.4% /0 for OI vs. 3.5%/ 6.4% for the spontaneous group), hypoglycemia (4.2% /7.6% for ART vs. 1.4% /1.5% for OI vs. 3.5% /4.5% for the spontaneous group), jaundice (28.4% /30.4% for ART vs. 20.3% /14.9% for OI vs. 27.0% /26.4% for the spontaneous conception group), and malformations (1.9% /3.2% for ART vs. 0 /3.0% for OI vs. 2.6% /1.8% for the spontaneous group). Furthermore, the incidence of respiratory disorders (RDS, transient tachypnea of the newborn, pneumothorax, and any unspecified respiratory difficulties that required ventilation) was comparable between groups (7.4% /12% for ART vs. 4.3% /6.0% for OI vs. 12.4% / 11.8% for the spontaneous group), same as orthopedic disorders including (congenital hip dislocation, bone fractures, and hip subluxation) (5.3% /3.3% for ART vs. 1.4% /3.0% for OI vs. 4.4% /3.6% for the spontaneous group), and other complications including (neurologic complications; hypotonus, hypertonus, and convulsions), intraventricular hemorrhage (IVH), Erb's palsy, sepsis, fever, and other metabolic complications (11.6% /16.3% for ART vs. 0/0 for OI vs. 2.6% /0 for the spontaneous group). Neonatal deaths were observed more frequently among the second twin of the ART group than the other groups (1.1% /2.2% for ART vs. 0 (0.0%) for OI vs. 2.6% /0 (0.0% for the spontaneous group).

#### **2.4.2. Neonatal outcomes of triplets and quadruplets according to the method of conception (spontaneous, MAR)**

Umero et al. (2011) studied the neonatal outcomes of 21 sets of triplets and one set of quadruplets after spontaneous conception. Study variables included gestational age at delivery, birth weight, fetal gender, fetal presentation and the neonatal morbidity. The mean and median gestational age was 32.4 weeks; except for one case delivered with gestational age  $\geq 37$  weeks. The mean birth weight in this study distributed as the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> triplets was (1,850, SD 880 g vs. 1,828, SD 791 g vs. 1,377, SD 1,032 g, respectively); only 5 neonates were delivered with normal birth weight. Fetal gender distribution showed that 54.0% were males. The arrangements of two females with one male were predominant 52.4%. There were six same-gender triplet sets (five all males and one all females). Fetal presentation was cephalic in 57.1% of the first triplet, 42.9% of the second triplet and 33% of the third triplet. Furthermore, in this study, among the 55 live triplets, 52 (94.5%) were admitted into the NICU mainly for prematurity and (90.9%) for low birth weight. Other indications for NICU admissions were; RDS (49.1%), birth asphyxia (25.5%), presumed neonatal sepsis (18.2%) and neonatal jaundice (34.5%). Perinatal mortality rate for the triplets was 276 in 1000 live births. Stillbirth reported in 8 (12.7%), early neonatal death was 5 (7.9%), while late neonatal death was 4 (6.3%). For quadruplet birth, the outcome was 2 females and 2 males; their birth weight was 1,300-1,600 g. All the neonates had good Apgar scores at birth but were admitted into the NICU due to prematurity and low birth weight. They were discharged home four weeks post-delivery with good conditions.

Fennsey et al. (2015) studied the neonatal outcomes of triplets following ART and spontaneous conception between January 1999 and February 2011, and found similar mean gestational age in the two groups (31.5, SD 2.9 weeks for the ART group vs. 31.3, SD 3.9 weeks for the spontaneous conception group), as well as similar mean birth weight (mean 1,521, SD 610 g for ART vs. 1,523, SD 563 g for the spontaneous group). The difference was not significant between the two groups in terms of respiratory distress syndrome (55% of the ART vs. 45% of the spontaneous group), as well as in the respiratory distress treatments with surfactant and the assisted ventilation and in the duration of stay in the NICU (median 17 days, 25<sup>th</sup> -75<sup>th</sup> centiles; 6.6 to 22 days for the ART group vs. 10 days, 25<sup>th</sup> -75<sup>th</sup> centiles 6 to 27 days for the spontaneous group). The other neonatal complications were equally uncommon between groups including IVH (1% in the ART vs. 0.0% in the spontaneous), bronchopulmonary dysplasia (0.0% vs. 4%, respectively), necrotizing enterocolitis (1% vs. 1%, respectively). The neonatal death rate was similar in the groups; it was found in 2 (3%) in the ART and 5 (6%) in the spontaneous group.

In Italy, Zuppa et al. (2007) performed a study to compare the neonatal outcomes of 6 triplets resulting from spontaneous conception and 18 triplets resulting from medically assisted conception (seven triplets were conceived by OI, eight by IVF, two by ICSI and one by gamete intra fallopian transfer). Results showed similar mean gestational age (33 weeks of both groups). In addition, no difference was found as well in the incidence of gestational age of  $< 32$  weeks (33.3% for spontaneous vs. 37.8% for medically assisted

conception group) and the gestational age between 32 to 36 weeks (66.7% vs. 62.2%, respectively). The mean birth weight in both groups was also comparable (1,760, SD 256 g for the spontaneous vs. 1,907, SD 452 g for the assisted group). There was no difference in the birth weight  $\leq 1,500$  g (11.1% vs. 11.3%, respectively), or birth weight between 1,501 to 2,500 g (88.9% vs. 88.7%, respectively). Furthermore, no significant difference was also noted between groups in terms of small for gestational age (16.7% of the spontaneous group vs. 5.7% of the medical assisted conception group), birth weight discordance  $>25\%$  (50.0% vs. 33.3%, respectively), slight depression at birth (27.7% vs. 20.7%, respectively), severe depression (22.2% vs. 14.1%, respectively), respiratory disease (5.5% vs. 7.5%, respectively), infections (16.6% vs. 15.1%, respectively), and the frequency of newborns who were affected by  $\geq 2$  diseases (5.5% vs. 11.3%, respectively). Patent Ductus Arteriosus (1.9%) was found in the medical assisted conception group, as well as fetofetal transfusion syndrome (1.9%), IVH (3.8%), stillbirth (one case) and malformation (3.8%).

In Israel, in a study performed by (Friedler et al., 1994) to examine the perinatal outcomes of 56 triplets following ART, 55 following OI by gonadotropins (GN), 27 by clomiphene citrate (CC), and 13 were conceived spontaneously. The newborns in the medical assisted conception groups had lower mean gestational age (33.2 weeks. for ART, 33.4 weeks. for GN, 34.2 weeks for CC, and 35.3 weeks for spontaneous conception), as well as the mean birth weight (1,743 g for ART vs. 1,683 g for GN vs. 1,863 g for CC vs. 1,963 g for spontaneous group). The incidence of very low birth weight was found higher in the medical assisted conception group (30.6% of the ART group vs. 30.3% of the OI by GN vs. 10.3% of the spontaneous group). No difference was noted between groups in terms of the incidence of low birth weight and perinatal mortality rate (77.9 for ART, 60.6 for GN, 111.0 for CC, and 25.6/1000 for spontaneous group).

Lipitz et al. (1993) studied the neonatal outcomes of 81 triplets (after ovulation induction, IVF, and spontaneous conception). Abstract data showed similar results in the neonatal outcomes in the ovulation induction and IVF groups, and there was also no significant difference in the neonatal mortality in the three study groups.

## **Summary**

This chapter presented the prevalence of multiple births, type of conception, as well as the maternal, obstetrical and neonatal outcomes according to type of conception at the international and national levels. Most research investigates the effect of method of conception on twin pregnancies, whereas little research investigates the effect on triplet and other higher-order pregnancies, it may therefore be advantageous to also investigate the effect of methods of conception on higher-order multiple pregnancy by extending the number of observations in this group of multiple births. Through literature review we found that multiple births constituted around 3% of all births globally. Prevalence of twins and higher-order multiple births was available in some countries which showed that 3.3% of births were twins and 0.1% were higher-order multiple births, whereas it was lacking in other countries. The prevalence of multiple births after spontaneous conception varies

worldwide, with the more frequent occurrence of twins and rare occurrence of higher-order multiples, consequently information about the prevalence is scarce. Twin births after spontaneous conception vary with the highest prevalence in African countries and the lowest in Asian countries. The occurrence of multiple births is very common after MAR, which was more frequently found among older women, lower parity and higher rate of infertility in the majority of the studies. According to pregnancy and neonatal outcomes of multiple births, there has been much research and discussion conducted to analyze the effect of methods of conception on the mothers with twins and also on twin neonates. Some studies showed inconsistent results, some studies showed a higher risk of adverse perinatal and neonatal outcomes after medically assisted conception, whereas others reported similar outcomes and others found a better perinatal outcome after the medically assisted conception. For the higher-order multiple pregnancies, a conflict with a lack of deep analysis was found. Almost all of the reviewed studies showed insignificant differences between groups in the maternal and neonatal outcomes and few studies showed lower mean gestational age and lower mean birth weight in the MAR group. But overall, all of the reviewed studies showed that multiple births pregnancy has a high risk of complications and health consequences on both the babies and their mothers.

## **Chapter three**

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### **Research Methodology**

#### **Introduction**

This chapter specifies the steps used to carry out this study. It includes study design, study population, variables of the study, the instrument development, validity of the study instrument, eligibility criteria, study setting, data collection procedure, limitations of the study, data analysis procedures and ethical consideration.

#### **3.1 Study design**

Polite and Beck (2006, p. 203) defined the research design as the researcher's overall plan for answering research questions. This retrospective study was held to investigate multiple births of all orders (twins, triplets and other higher-order multiples) that was approved by the board of graduate studies of Al-Quds University and by the Ministry of Health (MOH). A retrospective design is a design in which a phenomenon existing in the present time is linked to a phenomenon that occurred in the past, before the study was initiated (Polite & Beck, 2006, p. 188), and it is considered as the preferred design to study the rare occurrences (Hess, 2004). In this study, the retrospective design was used by the researcher to determine the prevalence of multiple births in the West Bank and its proportion by mode of conception. The design was also used to describe the maternal and neonatal outcomes in terms of morbidity and mortality through reviewing the medical records of the mother and her babies, by using a questionnaire in the five selected hospitals (two private and three public hospitals) distributed in north, center and south of the West Bank (WB) in the period between January 1<sup>st</sup>, 2010 and December 31<sup>st</sup>, 2011. Important and necessary information was retrieved from each of the records of the babies' mothers, and was filled by the researcher herself.

#### **3.2 Study population**

All consecutive multiple pregnancies delivered at  $\geq 24$  weeks of gestation in the selected five hospitals distributed in north, center and south of the West Bank between January 1<sup>st</sup>, 2010 and December 31<sup>st</sup>, 2011 were included in this study. A total of 912 multiple births were identified. Out of the 912; 820 were twin births, 92 were HOM births (86 were triplet

births and 6 were quadruplet births). Out of these births; a total of 896 multiple deliveries (808 twin births and 88 higher-order multiple births (82 triplets, and 6 quadruplets) were taken into account after exclusion criteria. A total of 1591 twin neonates and 262 triplet and quadruplet neonates were investigated in this study.

### **3.3 Eligibility criteria**

All live born multiple births (twins, triplets, and quadruplets) with  $\geq 24$  weeks of gestation were included in this study. Deliveries with less than 24 weeks of gestation were excluded from the study because these deliveries were considered as abortion cases and the fetuses delivered at that gestational age are usually nonviable and they will not be able to survive outside the uterus (Pillitri, 1999, p.373). Data with unknown gestational age and multiple births located outside of the West Bank were excluded from this study. In our study, three pairs had a gestation age less than 24 weeks (one birth in twins group and two births in triplets group), one triplet birth transferred from Gaza, and 12 pairs were found with unknown gestational age. In this study, a total of 896 deliveries (808 twins, and 82 triplets and quadruplets births) fulfilled the inclusion criteria.

### **3.4 Study setting**

Five hospitals in the WB namely (Alia, Rafidia, Palestinian Medical complex, Red Crescent, and Specialized Arab hospital) and one hospital in Jerusalem namely (Al-Maqassed hospital) were targeted. Five hospitals in the WB responded and agreed to offer their medical records of multiple births between January 1<sup>st</sup>, 2010 and December 31<sup>st</sup>, 2011, whereas Al-Maqassed hospital in Jerusalem did not respond, therefore it was excluded from the study. Among the five targeted hospitals in the WB, there were three public and two private hospitals. The public hospitals were; Alia in Hebron south of the WB, Palestinian Medical Complex in Ramallah center of the WB, Rafidia in Nablus north of the WB. Private hospitals were the Red Crescent Hospital in Ramallah center of the WB and the Specialized Arab Care Hospital in Nablus north of the WB. We targeted the main hospitals that provide good services in the West Bank who happen to have integrated neonatal units, and have frequent deliveries at their location. In addition to the mentioned above, the majority of Palestinians have health insurance which provides financial coverage for birth at these hospitals. Furthermore, these hospitals were highly recommended by experts who confirmed that the majority of the multiple birth cases will be found in these hospitals.

### **3.5 Variables of the study**

The case definition of “multiple births” was twins, triplets and quadruplets as other higher-order births were not recorded during the study period.

#### **3.5.1. The maternal variables were grouped into the following four sub-categories**

##### **3.5.1.1. Socio-demographic variables include:**

- Age (years): mother's age was grouped into <20, 20-24, 25-29, 30-34, 35-39, and 40-45. Missing 1 (0.1%) for twins, and 1 (1.2%) for triplets.
- Education (years): mother's education was categorized as follows: Unknown, Illiterate, Elementary, Preparatory, Secondary, Associate Diploma, Bachelor and above. Data was collected and cases were re-coded and grouped into three major groups: basic, secondary, and higher level of education. Missing data was 137 (17.0%) for twins, and 17 (20.7%) for triplets.
- Work status: mother's work status was categorized as follows: Unknown, Employed, Worker, Artisan, Business owner, Housewife, and Student. These categories were re-coded and categorized as housewife, employed, and student. Missing data was 71 (8.8%) for twins, 14 (17.1%) for triplets.
- Consanguinity: parental consanguinity was categorized as follows: Unknown, first cousin, second cousin, distant relative, not related. These were re-coded and categorized as relative, and not relative. Missing data was 170 (21.0%) for twins, and 18 (22.0%) for triplets.
- Place of residence: mother's place of residence was categorized as follows: South of West Bank, center of West Bank, and north West Bank. Data was complete for this variable.
- Type of hospital: it was categorized as public or private. Data was complete for this variable.

### **3.5.1.2. Health related variables include:**

- Previous medical history: medical history was categorized as follows: Unknown, No, Yes (type of medical diseases was specified if the answer was yes). The medical variable included medical diseases prior to pregnancy. Missing data was 53 (6.6%) for twins, and 9 (11.0%) of triplets.
- Cervical stitch placement: it was categorized as follows: Unknown, No, Yes. Missing data was 53 (6.6%) for twins, and 10 (12.2%) for triplets.
- Obstetric history: it was categorized as follows: Parity, and Abortion. Parity was grouped into (parity 0; no previous deliveries), (parity 1; one previous delivery (parity  $\geq 2$ ; two and more previous deliveries). Missing data was 1 (0.1%) for twins, and 1 (1.2%) for triplets. Abortion was categorized as follows: Unknown, No, Yes. Missing data concerning abortion was 1 (0.1 %) for twins, and 1 (1.2%) for triplets.
- Previous history of multiple births. Missing data was 102 (12.6%) for twins, and 15 (18.3 %) for triplets.
- Family history of multiple births. Missing data was 186 (23.0%) for twins, and 19 (23.2%) for triplets.

### **3.5.1.3. Pregnancy variables include:**

- Pregnancy outcomes: was categorized as follows: Twins, Triplets, Quadruplets, and Quintuplets or more.
- Mode of conception: was categorized as follows: spontaneous conception, medical assisted conception (infertility), medical assisted conception (no infertility), medical assisted conception (unspecified cause), and unspecified mode of conception. Data was re-coded and categorized as spontaneous conception, medical assisted conception, and unspecified mode of conception. Missing data was 108 (13.4%) of twins, and 8 (9.8%) of triplets.
- History of infertility: data collected was re-coded and categorized as Yes, No, and Unspecified. Missing data regarding the history of infertility in the medical assisted group was found in 13 (5.9%) of twins and 8 (12.7%) of triplets.
- Type of infertility: was categorized as follows: Unknown, Primary, and Secondary. Missing data was 2 (1.4%) for twins and 1 (2.2%) for triplet.
- Type of medical assisted reproductive treatment: was categorized as follows: IVF, IUI, and Drug stimulation also known as Induction of Ovulation (IOO). Missing data was 2 (1.4%) for twins.
- Fetus reduction. Missing data was 178 (22.0%) for twins, and 18 (22.0%) for triplets.
- Maternal and obstetrical complications include all complications recorded in medical records. Missing data was 43 (5.3%) for twins, and 8 (9.8%) for triplets.

### **3.5.1.4. Delivery variables include:**

- Delivery mode: was categorized as follows: Unknown, Vaginal, Instrumental (vacuum, forceps), cesarean section, and others/specify. These were re-titled as unknown, vaginal (spontaneous, instrumental), cesarean section, and mixed. Missing data was 8 (1.0%) for twins.
- Cesarean section delivery was classified as follows: Unknown, elective, and emergency. Missing data was 41 (8.6) of twins, 11 (14.0%) of triplets.
- Complications for the mother post-delivery mainly incidence of postpartum hemorrhage. Missing data was 49 (6.1%) for twins, and 8 (9.8%) for triplet.

### **3.5.2. The neonatal outcome variables include:**

- Gestational age (weeks): gestational age was categorized as follows: gestational age <32 weeks, 32-36 weeks, and  $\geq 37$  weeks.
- Birth weight (gram): birth weight was categorized as follows: birth weight <1000g, 1,000-1,500g, 1,500-2,500g and  $\geq 2,500$ g. Missing data was 9 (0.6%) for twins, and 1 (0.4%) for triplets.
- Birth weight discordance: was defined as a difference in birth weight of <15%. It was grouped into <15% discordance (concordant birth weight), 15-19.9% (mildly

discordant), 20-24.9% (mildly discordant), and  $\geq 25\%$  (severely discordant) (Blickstein & Kalish, 2003).

- Gender: was categorized as male, female, same sex sets and different sex sets. Missing data was 2 (0.1%) for twins.
- Apgar score: was grouped into  $<7$  and  $\geq 7$  at 1 and 5 minutes at delivery. Missing data at one minute was 24 (1.5%) for twins, 6 (2.5%) for triplets. Missing data at 5 minutes was 57 (3.6%) for twins, and 6 (2.5%) for triplets. Scores of ( $<7$ ) is considered as a low Apgar score.
- Neonatal complications include: prematurity (gestational age  $<36$  weeks), birth weight  $<2,500$ g, the need for NICU admission, and the major neonatal morbidities recorded in the medical records. Missing data was 32 (2.0%) for twins.
- NICU admission: was categorized as follows: Unknown, No, Yes. Missing data was 63 (4.0%) for twins, 14 (5.9%) for triplets.
- Data regarding indications of NICU admission was available for (n=442/659, 67.1%) of twins, among those (n=256/373, 68.6%) of twins in the SC group and for (n=159/221, 71.9%) of twins in the MAR group. For triplets, this data was available for (n=172/213, 80.8%), among those (n=27/29, 93.1%) in the SC group and (n=134/166, 80.7%) in the MAR group. For quadruplets, this data was also available for (18/23), among those (100% in the SC group), and (n=10/15 in the MAR group).
- Length of hospital stay is defined in the study as the period between the date of birth and the date of discharge. Missing data was 38 (5.8%) for twins, 7 (3.3%) for triplets, and 1 (4.3%) for quadruplets.
- Congenital anomalies were diagnosed by clinical examination of the neonate. Data was missing for 129 twins, in addition 55 cases had anomalies but data was not reported in the medical records. Data was missing for 35 triplets as well as four cases who had anomalies but data was not reported in the medical records. Patent ductus arteriosus was not considered as an anomaly except in two cases that were found with other anomalies. According to the National Birth Defects Prevention Network; patent ductus arteriosus in preterm newborns is considered as a consequence of prematurity not an inherent anomaly (Sever, 2004).
- Newborn's outcomes: was categorized as follows: Dead, Alive, and Unknown. This variable was analyzed into perinatal and neonatal mortality. Missing data was 94 (5.9%) for twins, and 20 (8.4%) for triplets. Data regarding the newborns' outcomes (alive or dead) after neonatal period was reported for 12 (0.8%) newborns of twins and 8 (3.3%) of triplets.

### **3.6 Study instrument**

The instrument of the data collection for this study was a structured questionnaire (please refer to annex 2) designed by the researcher with referring to the literature and the gynecologists working in the field of reproduction and infertility treatments and with guidance of the supervisor. Some items in the questionnaire are open-ended questions and other close-ended questions. The questionnaire was developed in a detailed form to get

more insight about the multiple births. Therefore, we could not analyze all the data collected because it was a large data. As a result, the focus of the analysis was on the major study components. Information

The questionnaire consisted of two parts:

**Part One:** Mother's information. It has a total of 50 items;

- Identification information which included five categories: place of residence, type of hospital, name of hospital, hospital record number, and admission date.
- Socio-demographic information which included seven categories: mother's age, education, and occupation. In addition, husband's education, occupation, and parental consanguinity was obtained.
- Health history which included 12 categories: mother's blood type, body mass index, smoker/smoking during pregnancy, previous medical history, previous surgical history, and exposure to oral contraceptive before latest pregnancy, obstetric history, personal and family history of multiple births.
- Latest pregnancy variables which included 11 categories: date of last menstrual period, mode of conception, history and type of infertility, causes of infertility, type and number of medical assisted reproductions, number of fetuses inserted in case of IVF, fetal reduction, vanishing twin, pregnancy outcomes, and complications during pregnancy.
- Antenatal care which included five categories: antenatal visits dates, the use of Corticosteroids injection during pregnancy, the use of hormonal supplement during pregnancy, detailed ultrasound, and triple test.
- Delivery variables which included 10 categories: type of labor, duration of labor, rupture of membrane, complications during delivery, delivery date, delivery time, delivery mode, type of instrumental delivery, classification of cesarean section (elective & emergency) and complications for the mother post-delivery.

**Part Two:** Newborns' information, made up of 15 categories;

- Newborns' characteristics including: gender, birth weight, blood group, Apgar score at one and five minutes, fetal presentation, and chorionicity;
- Neonatal morbidities;
- Length of hospital stay;
- Readmission of newborns to hospital during the study period;
- Newborn's outcomes; and
- Finally, the last three categories aimed to assess the presence of abnormality, if it is minor or major. In addition, the details category aimed to assess the types of abnormality, family history of abnormality, cause of newborns' death, and death during infancy.

### **3.6.1 Validity of the study instrument**

Validity is defined as the degree to which an instrument measures what it is supposed to measure (Polite & Beck, 2006, p. 340). The study questions were developed by the

researcher based on the study objectives and published literature about multiple births. The content validity is concerned with the sampling adequacy of the content being measured. Experts' judgments can be used to evaluate whether the items of the instrument adequately measure all the study variables (Polite & Beck, 2006, p. 329). The study instrument was evaluated and approved by the different experts including researchers, neonatologists, and obstetricians (please refer to annex 1). The researcher's thesis advisor also assessed the instrument for wording, adequacy, and coverage of items for the study objectives. No reliability nor piloting testing was done, but data from the medical records was assessed and evaluated for adequacy and missing items. Furthermore, there was an agreement between maternal recalling and records data regarding pregnancy and birth. Vonkoss, Moore, and Richredson (1995) mentioned that the documentation in the medical records is considered to be legally and medically accurate and reliable.

### **3.7 Data processing description**

#### **3.7.1. Designing the tool of research and indicators development (the questionnaire)**

The researcher developed the questionnaire based on the objectives of the study. The objectives of the study are transferred to measurable indicators, which are used in designing the questions of the questionnaire. In designing the questionnaire, the researcher took into consideration providing a literature review on all available previous studies related to the subject of the study in order to identify and use all the indicators and variables that might affect the study. Questionnaire with open-ended items were developed for data collection because it was challenging to make close-ended questions as some of the information written in the patients' notes available in the medical records was narrative.

#### **3.7.2. Data collection**

Data were obtained by the researcher herself by reviewing the women's and neonates' medical records and birth registries in each targeted hospital in the period between January, 2010 and December, 2011. Data was collected after taking a written consent from the MOH to review the medical records from the public hospitals, whereas in the private hospitals; the medical records were reviewed after taking a written consent from the hospital managers. Maternal data was collected from the case records including the demographic details, health history, pregnancy and delivery details, and complications of pregnancy. Neonatal data was collected from the case records including the conditions of the neonates at birth, and the progress in the NICU for the cases that required care.

Data collection process was lengthy; arduous, and challenging; because the medical records were gathered and prepared for data collection through a complex process that required reviewing the birth registries and the hospital admission registries, to obtain the cases of multiple births by the researcher, in addition to the inspection of the medical records from three selected hospitals by the researcher herself because the employees were occupied with other work. Also, traveling to Alia Hospital in Hebron and Rafidia Hospital in Nablus was time consuming as the destination was far and the researcher had one day per week to gather and collect all the necessary data. Moreover, the data in the majority of

medical records in the five selected hospitals was not satisfying; some of the required data about multiple births was not completely documented in the medical records. Some of the lacking data for some cases were, the mothers' and their husbands' education and work status, parental consanguinity, family monthly income, mother's body mass index, history of smoking during pregnancy, exposure to oral contraceptive before last pregnancy, personal and family history of multiple births, causes of infertility, sex selection, and the fetuses reduction. Data regarding number of trials for the latest attempt of medical assisted reproduction, fetuses inserted in case of IVF, vanishing twin, and the antenatal care (including: antenatal visits, using of corticosteroids injections and hormonal supplement during pregnancy, detailed ultrasound and triplet test) was not available in all of the medical records in all of the selected hospitals as well. Furthermore, data about the mode of conception was not also completely available for all cases of multiple births; it was more frequently recorded for cases that used the MAR. Since there was incomplete data about some of the needed variables, mothers were contacted by phone to retrieve answers about the missing variables. The researcher was able to contact the majority of them.

### **3.7.3. Data auditing and reviewing**

After all the collected data was checked and reviewed, the next step was to begin the data entry. After reviewing the data collected by the statistician, he suggested to develop more structured questionnaire as the data was collected using open-ended questions which is more challenging for data entry. This would ensure that data will not be lost and data processing and analysis would be easier. Therefore, a structured questionnaire was developed. The collected data was put into the structured questionnaire and it was ready for data entry.

### **3.7.4. Data coding**

During this process, all open questions are post coded by the editors, some answers were grouped together either by the topic or by the type. The post coding process is important for transforming open questions into close-ended questions to make the data analysis process faster and easier. All of the coded variables were reviewed by the researcher to minimize errors and to maintain consistency.

### **3.7.5. Data entry**

Logical checks and control rules were defined by the statistician to minimize data entry errors and to ensure unbiased and reliable results.

### **3.7.6. Data cleaning**

Data cleaning is a very essential step before data analysis which aims at detecting any data errors. This process was done by cross validation of results through conducting various cross tabulations and if an error is detected, the whole questionnaire was re-entered.

### **3.7.7. Data analysis procedures**

The data collected in a study does not by itself answer research questions or test research hypothesis (Polite & Beck, 2006 p.351). Data needs to be systematically analyzed so that trends and patterns can be detected (Polite and Beck, 2006 p.351). After data collection, the compiled data was refined, entered and analyzed using the Statistical Package for Social Science Program (computer software SPSS version 23). Tables were formulated for the study variables. Demographic and outcomes data were analyzed in three ways. First, data was analyzed for all the multiple births  $\geq 24$  weeks of gestation regardless of the mode

of conception. Second, medically assisted conceived multiple births (including IVF, IUI, and IOO) were compared to those spontaneously conceived. Third, comparisons were made according to the type of MAR, i.e., IVF-conceived multiple births vs. IUI conception vs. conception after IOO. Placental chorionicity is the important factor that may affect the outcomes of multiple pregnancies. In this study, as we do not have complete information on the chorionicity, hence, we were unable to analyze the outcomes in relation to chorionicity.

Prevalence of multiple births was calculated by using the formula:

$$\frac{\text{Total multiple births} \times 100}{\text{Total births}}$$

Prevalence of multiple births after spontaneous and medical assisted conception was calculated by using the formula:

$$\frac{\text{Number of multiple births after spontaneous or medical assisted conception} \times 100}{\text{Total multiple births}}$$

Inter-pair difference in birth weight was calculated by using the formula for newborns (twins, triples or quadruplets):

$$\frac{\text{Heavier twin weight} - \text{Lighter twin weight} \times 100}{\text{Heavier twin weight}}$$

Perinatal mortality rate was calculated using the formula:

$$\frac{\text{The number of perinatal deaths} \times 1000}{\text{Total number of births (stillbirths + live births)}}$$

Neonatal mortality rate was calculated using the formula:

$$\frac{\text{The number of deaths during the first 28 days of life} \times 1000}{\text{Total number of live births}}$$

The early neonatal mortality rate was calculated using the formula:

$$\frac{\text{The number of neonatal deaths 0-7 days} \times 1000}{\text{Total number of live births}}$$

The late neonatal mortality rate was calculated using the formula:

$$\frac{\text{The number of neonatal deaths after 7-28 days} \times 1000}{\text{Total number of live births}}$$

### **Total number of live births**

Statistics such as percentages, mean, median, minimum and maximum values, standard deviation, graphs, and Cross-tabulation were used to describe the distribution of and relationship among variables.

### **3.8 Ethical consideration and accessibility**

Ethical approval for the study was obtained from the board of Higher Studies Council at Al-Quds University, and from the Palestinian MOH. Also, approval for the study was obtained from the hospital managers in private hospitals. Confidentiality was taken into consideration regarding data obtained from medical files. The cases were kept anonymous during data collection and analysis. In addition, mothers' hospital record number was the reference for data management.

### **3.9 Limitations of the study**

A number of limitations are worth noting. This was a retrospective study conducted from five selected hospitals which could compromise the generalizability of the findings.

There were significant obstacles in performing this study.

- One of the most important limitations of this study was limited national and international studies (Thesis or Journals) that were concerned about studying maternal and neonatal outcomes of multiple births, in particular the higher-order multiple births.
- The main resource for related literature was the Pub Med website, which provides a limited number of full text articles. Whereas, the majority of the available literature in this website was abstract data.
- The researcher had difficulty accessing medical records in the medical records department due to the fact that the employees were occupied with other work. As a result, the researcher had to inspect and gather data from the medical records by herself, hence causing delay in the data collection timeline.
- Socio-demographic and obstetrical background information was not available in the majority of the medical records in the five selected hospitals. Moreover, there were no antenatal care records for the majority of mothers in the five selected hospitals; this is because those mothers had their routine follow-up during pregnancy in private clinics.
- During filling the questionnaire from the medical records, the researcher faced difficulties in reading some files and in explaining some terms, so she received assistance from one of the doctors working in the hospital.

However, since literature concerning maternal and neonatal outcomes of twins and higher-order multiple births resulting from non-IVF fertility treatments is scarce, this study

enriches the literature concerned with this topic. Also, this study enriches the limited literature regarding the outcomes of the higher order multiple births spontaneously conceived or those resulting from MAR. In addition, this study provides important baseline data to guide future work in a country that has a high incidence of medically assisted conceived higher-order multiple births and to anticipate the perinatal problems that will increase due to prematurity and low births weight, also to anticipate the scope of perinatal care that may be required by multiple births.

## **Summary**

The research design was a retrospective design to determine the prevalence of multiple births, its proportion by mode of conception (spontaneous vs. MAR) in the selected five hospitals in the WB, and to identify the maternal and neonatal outcomes of these births. The researcher targeted all women who delivered two or more newborns in five selected hospitals in north, middle and south of the West Bank. There were 912 multiple births deliveries, which consisted of 819 twin deliveries, 86 triplets and 6 quadruplets deliveries. Data was collected through using a questionnaire. The study instrument was constructed by the researcher and used for the first time. It was validated by experts and researchers in the field of reproduction. Data was analyzed for all the live born multiple births with gestational age  $\geq 24$  weeks. For data analysis, the researcher utilized the SPSS program, descriptive statistics was used, means and standard deviations were computed, percentages and cross tabulation were used as well. Limitations of the study included narrow generalizability of the study findings, in addition to limitations related to implementations of the study including limitation of national and international studies, studies regarding multiple births were not fully explored in the literature, difficulties in accessing the medical records, insufficiency of information in the medical records, and difficulties in reading some files and in explaining some terms.

## Chapter Four

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### Analysis and Findings

#### Introduction

This chapter presents in detail the main findings of the study in accordance with the study objectives using descriptive analysis. The data includes prevalence of multiple births in the five selected hospitals, type of conception, population characteristics and pregnancy, childbirth and neonatal outcomes. For all of the assessed parameters, data was initially presented for all of the groups of multiple births and then data was compared according to method of conception.

#### 4.1 Prevalence of multiple births in the five selected hospitals

There was a total of 41,244 deliveries in the five selected hospitals during the two years of study period (January, 2010 to December, 2011) that were covered by this study. Of the 41,244 deliveries, 912 were multiple births (820 pairs of twins, 86 sets of triplets and 6 sets of quadruplets). This made an overall incidence of 22.1 per 1000 births (2.2%). No higher-order multiple births (HOM) beyond quadruplets were recorded. Among the multiple births, twin births represented 2.0% of all births and 89.9% of all multiple births. Higher-order multiple births (86 sets of triplets and 6 sets of quadruplets) accounted for 0.2% of all births and 10.1% of all multiple births. The incidence of triplets was 0.2% of all births and 9.4% of all multiple births. Quadruplet births represented 0.01% of all births and 0.7% of all multiple births.

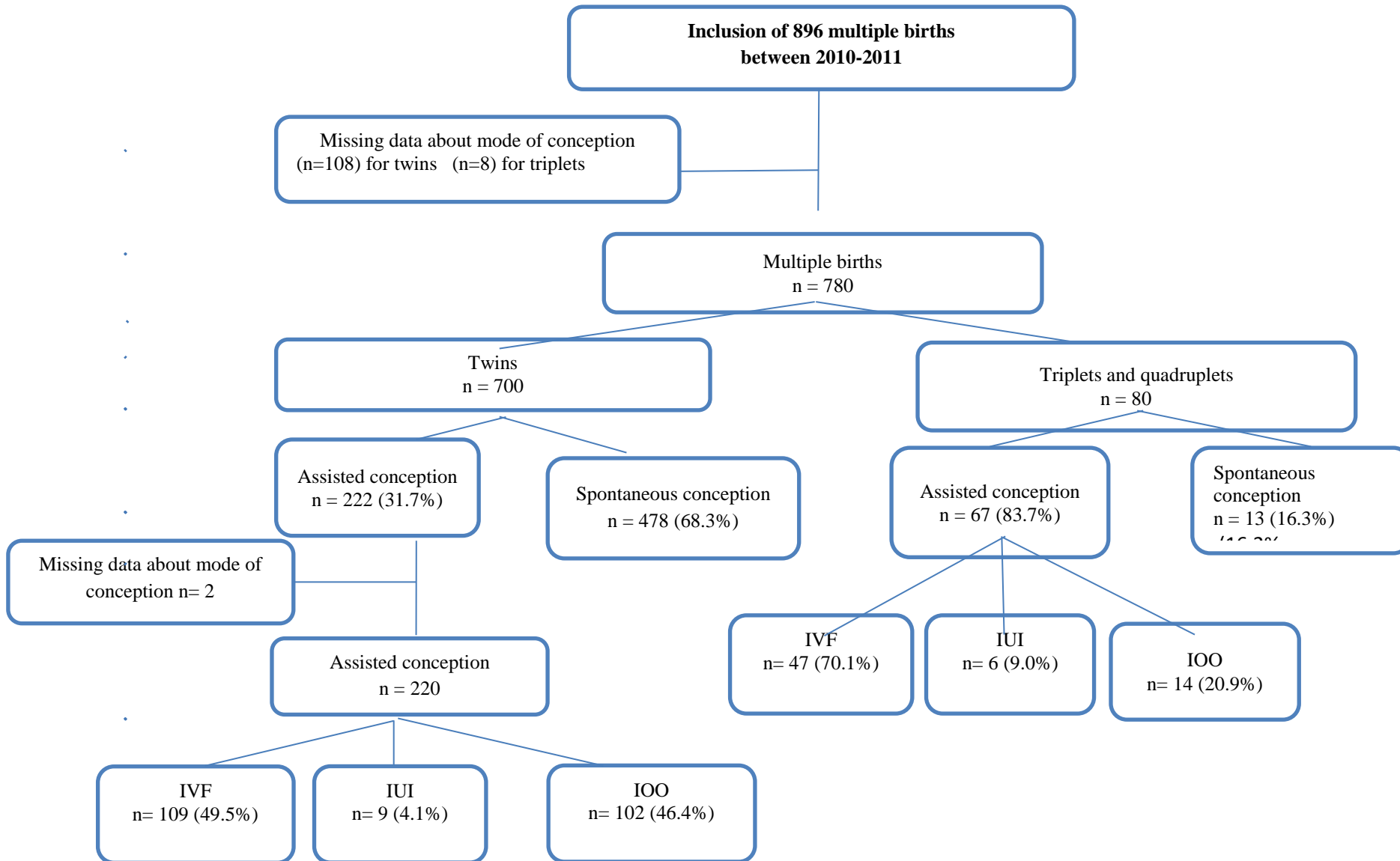
Table (4.1) presents the prevalence of multiple births at each of the five selected hospitals included in our study. Of these hospitals, the Specialized Arab Hospital had the highest prevalence of multiple births (10.3%), followed by the Alia hospital (2.4%), Rafidia hospital (1.9%), and the Palestinian Medical Complex (1.7%). The Red Crescent hospital had the lowest prevalence of multiple births (1.5%). Out of 912 multiple births, a total of 896 birth fulfilled the inclusion criteria (808 twin births and 88 higher-order multiple births; 82 triplets, and six quadruplets). Among the 808 twin births, there were 804 initial twin pregnancies and four multi fetal pregnancies reduced to twins. Among the 82 triplet births, there were 80 initial triplet pregnancies, and two multi fetal pregnancies reduced to triplets.

Table 4.1: Prevalence of multiple births in the five selected hospitals in the West Bank for a period of two years (2010-2011)

Hospitals	Total births	Total multiple births	Twin births	Triplet births	Quadruplet births
Alia	13,801	331(2.4%)	308 (2.2%)	21(0.2%)	2(0.01%)
Rafidia	11,377	213(1.9%)	196 (1.7%)	17(0.1%)	–
Palestinian medical complex	9,171	162(1.7%)	154 (1.7%)	8(0.09%)	–
Red Crescent	5,717	85(1.5%)	84 (1.5%)	1 (0.02%)	–
Specialized Arab hospital	1,178	121(10.3%)	78 (6.6%)	39(3.3%)	4(0.3%)

## 4.2 Methods of multiple births conception

Figure (4.1) presents the method of conception of multiple births. Out of the 896 multiple births sets, the method of conception is not known for 116 sets (108 for twins and 8 for triplets). Of the remaining 700 twin births sets, the rate of those conceived spontaneously was higher (n=478, 68.3%), and of the remaining 74 triplet births sets, the rate of those conceived by MAR was higher (n=63, 85.1%). Out of the six births of quadruplets, four were the result of MAR, and the remaining two were the result of spontaneous conception. Regarding the type of MAR, the most common type used in the twin group was IVF (49.5%), the second large group (46.4%) was a result of IOO, while the IUI was rare (4.1%). Among triplets; the IVF was also the most common type used (73.0%), (17.5%) were as a result of IOO, and the IUI was also rare in this group (9.5%). Out of four births of quadruplets, three sets were a result of IOO and the remaining one was after IVF.



**Figure 4.1: Methods of multiple births conception. IVF, In vitro fertilization, IUI, Intrauterine insemination, IOO, Induction of ovulation.**

## **4.3 Description of the socio-demographic characteristics, medical and obstetrical histories of women with multiple births**

### **4.3.1. Description of the socio-demographic characteristics of all of the women with multiple births**

This part of the analysis highlights the socio-demographic characteristics of the mothers who conceived multiple births including (mothers' age, education, and work status). Parental consanguinity, place of residence, and type of hospital (place of delivery) were described as well.

By looking at (Table 4.2) we observe that, the majority of the mothers of multiple births (twins and higher-order multiples) (755/807, 93.5%) are between 20 to 39 years, that means that the mothers of multiple births in our study were at a young age group, with peak incidence of 25 to 29 years for both twins group 30.5%, and triplets group 38.3%. Three of the six mothers (50.0%) of quadruplets are between 20 to 24 years. In this study, the minimum maternal age was found to be 17 years for twins, 19 years for triplets and 22 years for quadruplets and the highest maternal age was 45 years for twins, 39 years for triplets, and 35 years for quadruplets. The mean maternal age of twins was 27.9 years (SD 5.5), 27.9 years (SD 4.9) for triplets, and 27.8 years (SD 5.5) for quadruplets.

Secondary educational level was common accounting for 37.2% for women with twins, the other large group of women had a basic educational level at a rate of 34.6%, and the lowest was for those who had higher educational level at a rate of 28.2%. Among women with triplets, the higher educational level was the common accounting for 43.1%, 33.8% had secondary educational level and the lowest percentage was for those who had a basic educational level at a rate of 23.1%. Out of the six women with quadruplets, three (50.0%) had secondary education, two (33.3%) had basic education and the remaining one woman (16.7%) had higher education.

Our study has further showed that the majority of women with multiple births were housewives, (640/737, 86.8%) for twins, (55/68, 80.9%) for triplets, and (5/6, 83.3%) for quadruplets, and the majority of multiple births resulted from non-consanguineous marriage (421/638, 66.0%) of twins, (48/64, 75.0%) of triplets and (4/6, 66.7%) of quadruplets.

This study also showed that the rate of twins in the north and center of the WB was slightly different but lower than that in south of the WB (37.6% in the south vs. 32.1% in the north vs. 30.3% in the center). About half of triplets 53.7% (44/82) were seen among women reported living in the north of the WB, 28.0% were seen among women reported living in the south of the WB, triplets' rate was the lowest (18.3%) for those reported living in the center of the WB. Among the six quadruplets, four (66.7%) were seen among women reported living in the north of the WB, and the remaining two (33.3%) were seen among women reported living in the south of the WB.

This study also indicated that the majority of twin deliveries (647/808, 80.1%) occurred in public hospitals. About half of triplet deliveries, 53.7% (44/82), occurred in public hospitals, the other nearly half of these deliveries occurred in private hospitals 46.3% (38/82). Among the six quadruplet deliveries, four births (66.7%) occurred in private hospitals.

Table 4.2: Socio-demographic characteristics of all multiple birth mothers

Parameters	Multiple births	
	Twins N=808	Triples and quadruplets N=88
<b>Maternal age (years)</b>	<b>N=807</b>	<b>N=87</b>
Mean (SD)	27.9 (5.5)	27.9 (4.9)
Minimum-maximum	17- 45	19-39
<20	43 (5.3%)	2 (2.3%)
20-24	206 (25.5%)	23 (26.4%)
25-29	246 (30.5%)	31 (35.6%)
30-34	187 (23.2%)	20 (23.0)
35-39	116 (14.4%)	11 (12.6%)
40-45	9 (1.1%)	—
<b>Mother's education †</b>	<b>N=671</b>	<b>N=71</b>
Basic	232 (34.6%)	17 (24.0%)
Secondary	250(37.2%)	25 (35.2%)
Higher	189 (28.2%)	29 (40.8%)
<b>Mother's work status</b>	<b>N=737</b>	<b>N=74</b>
House wife	640 (86.8%)	60 (81.1%)
Employed	77 (10.5%)	12 (16.2%)
Student	20 (2.7%)	2 (2.7%)
<b>Consanguinity</b>	<b>N=638</b>	<b>N=70</b>
Relative	217 (34.0%)	18 (25.7%)
Not relative	421 (66.0%)	52 (74.3%)
<b>Mother's place of residence (WB)</b>	<b>N=808</b>	<b>N=88</b>
South of WB	304 (37.6%)	25 (28.4%)
Center of WB	245 (30.3%)	15 (17.1%)
North of WB	259 (32.1%)	48 (54.5%)
<b>Type of hospital</b>	<b>N=808</b>	<b>N=88</b>
Public	647 (80.1%)	46 (52.3%)
Private	161 (19.9%)	42 (47.7%)

*Note.*

SD, standard deviation; WB, West Bank.

†Basic: first stage (grades 1-4), second stage (grades 5-9), and secondary: (grades 10-12) higher: it is the high stage of education served by universities.

More details on the maternal socio-demographic characteristics for triplets and quadruplets groups will be given in the annex 3.

#### **4.3.2. Description of the socio-demographic characteristics of women with multiple births according to the method of conception (spontaneous, MAR).**

The different socio-demographic characteristics for both groups (SC vs. MAR) are summarized in Table (4.3). Comparison was limited to twins and triplets. The small number of quadruplets was not compatible for comparison. Among twin groups, the mean maternal age for the spontaneous group was on average five months higher than the mean for the MAR group (mean 28.2 years, SD 5.9 for the SC group; minimum=17; maximum=45 vs. 27.8 years, SD 4.5 for the MAR group; minimum=17; maximum=39). The age groups of 25 to 29 years and 20 to 24 years were the most numerous categories in the SC group (27.4% vs. 26.8%, respectively), while the largest age group (39.2%) for the MAR group was that of 25 to 29 years. This result means that the mothers in both groups were at a young age.

The mothers of triplets in the SC group were older than those in the MAR (mean age 30.3 years, SD 4.9 in the SC group; minimum=23; maximum=37 vs. 27.3 years, SD 4.9 in the MAR group; minimum=19; maximum= 39). The largest age group (4/11, 36.4%) for the SC group was that of 30 to 34 years, while the largest age group (42.8%) for MAR group was that of 25 to 29 years.

Women with twins in the MAR group are more likely to have higher education than those in the SC group (37.1% of the MAR vs. 25.1% of the SC), and less likely to have secondary education (34.2% of the MAR vs. 38.2% of the SC) and basic education (28.7% of the MAR vs. 36.7% of the SC). Furthermore, among triplet groups, women with triplets in the MAR group are also more likely than those in the SC group to have higher education (50.0% of the MAR vs. 2/11, 18.2% of the SC) and less likely to have secondary education (28.8% of the MAR vs. 6/11, 54.5% of the SC) and basic education (21.2% of the MAR vs. 3/11, 27.3% of the SC).

The work status of women with twins varies slightly among the groups, with higher percentage of housewives in the SC group than in the MAR group (87.4% in the SC vs. 83.2% in the MAR), and a lower percentage of employed women in this group (9.9% of the SC vs. 14.4% of the MAR). Among triplet groups, there were more housewives in the SC group than in the MAR group (10/11, 90.9% of the SC vs. 77.8% of the MAR), and less employed women in this group (1/11, 9.1% of the SC vs. 18.5% of the MAR).

As regards to parental consanguinity, although the percentage of twins resulting after consanguineous marriage was low in both groups, it was higher in the SC group (36.6% of the SC vs. 28.0% of the MAR). The percentage of triplet neonates resulting after consanguineous marriage was also low in both groups (3/11, 27.3% of the SC vs. 25.0% of the MAR), however, it was slightly higher in the SC group.

Women with twins in MAR were more frequently reported living in north of the WB (37.4% of the MAR vs. 31.6% of the SC) and less frequently reported living in south of the WB (31.5% of the MAR vs. 38.1% of SC) compared to those in the SC group. Although women with triplets in both SC and MAR group were more frequently reported living in north of the WB (55.6% of the MAR vs. 5/11, 45.4% of the SC), the percentage was higher for those in the MAR group, whereas the percentage of triplets resulted after MAR was

lower among women reported living in center of the WB (17.5% of the MAR vs. 3/11, 27.3% of the SC).

The study also indicated that twin deliveries in the SC group were more likely than those in the MAR group to occur in public hospitals (85.6% of the SC vs. 62.6% of the MAR) and less likely to occur in private hospitals (14.4% of the SC vs. 37.4% of the MAR). Among triplet groups, deliveries in SC group were also more likely to occur in public hospitals than those in the MAR group (90.9% of the SC vs. 44.4% of the MAR group) and less likely to occur in private hospitals (1/10, 9.1% of the SC vs. 55.6% of the MAR).

Table 4.3: Socio-demographic characteristics of women with multiple births for the SC and MAR groups

Parameters	Twins		Triplets	
	SC N=478	MAR N=222	SC N=11	MAR N=63
<b>Maternal age (years)</b>	<b>N=478</b>	<b>N=222</b>	<b>N=11</b>	<b>N=63</b>
Mean (SD)	28.2 (5.9)	27.8 (4.5)	30.3 (4.9)	27.3 (4.9)
Minimum- maximum	17-45	17-39	23-37	19-39
<20	26 (5.4%)	8 (3.6%)	—	2 (3.2%)
20-24	128 (26.8%)	48 (21.6%)	2 (18.2%)	17 (27.0%)
25-29	131 (27.4%)	87 (39.2%)	2 (18.2%)	27 (42.8%)
30-34	99 (20.7%)	62 (27.9%)	4 (36.4%)	11 (17.5%)
35-39	86 (18.0%)	17 (7.7%)	3 (27.2%)	6 (9.5%)
40-45	8 (1.7%)	—	—	—
<b>Mother's education</b>	<b>N=455</b>	<b>N=202</b>	<b>N=11</b>	<b>N=52</b>
Basic	167 (36.7%)	58 (28.7%)	3 (27.3%)	11 (21.2%)
Secondary	174 (38.2%)	69 (34.2%)	6 (54.5%)	15 (28.8%)
Higher	114 (25.1%)	75 (37.1%)	2 (18.2%)	26 (50.0%)
<b>Mother's work status</b>	<b>N=476</b>	<b>N=208</b>	<b>N=11</b>	<b>N=54</b>
Housewife	416 (87.4%)	173 (83.2%)	10 (90.9%)	42 (77.8%)
Employed	47 (9.9%)	30 (14.4%)	1 (9.1%)	10 (18.5%)
Student	13 (2.7%)	5 (2.4%)	—	2 (3.7%)
<b>Consanguinity</b>	<b>N=443</b>	<b>N=193</b>	<b>N=11</b>	<b>N=52</b>
Relative	162 (36.6%)	54 (28.0%)	3 (27.3%)	13 (25.0%)
Not relative	281 (63.4%)	139 (72.0%)	8 (72.7%)	39 (75.0%)
<b>Mother's place of residence (WB)</b>	<b>N=478</b>	<b>N=222</b>	<b>N=11</b>	<b>N=63</b>
South	182 (38.1%)	70 (31.5%)	3 (27.3%)	17 (26.9%)
Center	145 (30.3%)	69 (31.1%)	3 (27.3%)	11 (17.5%)
North	151 (31.6%)	83 (37.4%)	5 (45.4%)	35 (55.6%)
<b>Type of hospital</b>	<b>N=478</b>	<b>N=222</b>	<b>N=11</b>	<b>N=63</b>
Public	409 (85.6%)	139 (62.6%)	10 (90.9%)	28 (44.4%)
Private	69 (14.4%)	83 (37.4%)	1 (9.1%)	35 (55.6%)

Note.

SC, spontaneous conception; MAR, medical assisted reproduction; WB, West Bank; SD, standard deviation.

### **4.3.3. Description of medical and obstetrical histories of all of the women with multiple births**

This part of the analysis highlights the health and the obstetrical histories of the women with multiple births. It includes (previous medical history, cervical stitch placement, and history of multiple births which includes (personal and family history), history of infertility, and obstetrical history which includes (parity and history of abortion).

We noted from (Table 4.4) that the majority of the women with multiple births had no previous medical history, (694/755, 91.9%) of twins, (68/73, 93.2%) of triplets and (5/6, 83.3%) of quadruplets. During the current pregnancy; cervical stitch was performed for 13.2% of the women with twins, and for the majority of those with triplets (51/72, 70.8%) and for (4/6, 66.7%) of those with quadruplets.

More than half of the women with twins had given birth more than twice 55.4% (447/807), the lowest percentage was for women who had given one birth (18.1%). For women with triplets, about half of them 51.9% (42/81) didn't give birth previously; the lowest percentage (22.2%) was for women who gave birth once. Of the six women with quadruplets, three (50.0%) had two or more previous births, two (33.3%) had no previous birth, and the remaining one (16.7%) had one previous birth.

Regarding the history of abortion, most women with multiple births had no history of abortion, (549/807, 68.0%) with twins, (62/81, 76.5%) with triplets and (5/6, 83.3%) with quadruplets. In the analysis of personal and family history of multiple births, we found that only 12.0% of women with twins and (9/67, 13.4%) of women with triplets reported having a personal history of multiple births, knowing that most of those women had a family history of multiple births. However, most of the women with multiple births had a family history of multiple births, (492/622, 79.1%) with twins (44/63, 69.8%) with triplets and (4/6, 66.7%) with quadruplets.

History of infertility was found in 20.5% of twins' group; primary infertility in this group was identified in 43.2% of the couples and 56.8% were found with secondary infertility. In the triplets group; most of the cases (45/66, 68.2%) had a history of infertility; of which 51.1% was due to primary infertility and 48.9% was due to secondary infertility. In the quadruplets group; four of the six couples had a history of infertility, two of the four couples (50.0%) had primary infertility, and the remaining two (50.0%) had secondary infertility (data regarding type of infertility was not shown in the analysis).

Table 4.4 Medical and obstetrical histories of all of the multiple birth groups

Parameters	Multiple births	
	Twins N=808	Triplets and quadruplets N=88
<b>Medical history†</b>	<b>N=755</b>	<b>N=79</b>
Yes	61 (8.1%)	6 (7.6%)
No	694 (91.9%)	73 (92.4%)
<b>Cervical stitch</b>	<b>N=755</b>	<b>N=78</b>
Yes	100 (13.2%)	55 (70.5%)
No	655 (86.8%)	23 (29.5%)
<b>Parity</b>	<b>N=807</b>	<b>N=87</b>
0	214 (26.5%)	44 (50.6%)
1	146 (18.1%)	19 (21.8%)
≥2	447 (55.4%)	24 (27.6%)
<b>Previous abortion</b>	<b>N=807</b>	<b>N=87</b>
Yes	258 (32.0%)	20 (23.0%)
No	549 (68.0%)	67 (77.0%)
<b>Previous history of multiple births</b>	<b>N=706</b>	<b>N=73</b>
Yes	85 (12.0%)	9 (12.3%)
No	621 (88.0%)	64 (87.7%)
<b>Family History of multiple births</b>	<b>N=622</b>	<b>N=69</b>
Yes	492 (79.1%)	48 (69.6%)
No	130 (20.9%)	21 (30.4%)
<b>Infertility</b>	<b>N=687</b>	<b>N=72</b>
Yes	141 (20.5%)	49 (68.1%)
No	546 (79.5%)	23 (31.9%)

Note.

†Includes respiratory, hepatic, endocrine, heart, hypertension, depression, rheumatoid arthritis, thalassemia, poliomyelitis, and others for twin group, hepatic, heart, thalassemia, varicose vein, allergy, and others for triplet group, and varicose vein for quadruplet group (please refer to annex 5).

More details on the medical and obstetrical histories of the women with triplets and quadruplets will be given in the annex 4.

#### 4.3.4. Description of medical and obstetrical histories of women with multiple births according to the method of conception (spontaneous, MAR)

Medical and obstetrical histories in both groups are displayed in (Table 4.5). Comparison was limited to twins and triplets. The majority of women with twins and triplets in both groups had no history of preexisting medical conditions. Among twin groups, the percentage was slightly higher in the SC group (445/478, 93.1% of the SC vs. 191/214, 89.3% of MAR), whereas among triplet groups the percentage was slightly higher in the MAR group (54/57, 94.7% of MAR vs. 10/11, 90.9% of the SC).

During the current pregnancy, the placement of cervical stitch was more common in the MAR group of twins (34.1% of the MAR group vs. 4.6% of the SC group), and triplets (77.2% of the MAR vs. 5/10, 50.0% of the SC).

As expected, women with multiple births conceived by MAR, medically assisted conceived multiple births tend to be with lower parity. For those with twins, the percentage of women who hadn't given birth before was higher in the MAR than in the SC group (45.5% of the MAR vs. 18.0% in the SC), as was the percentage of those who had given birth once (23.0% in the MAR vs. 16.3% in the SC). Whereas the proportion of those who had given births more than twice was low in this group (31.5% of the MAR vs. 65.7% of the SC). For those with triplets, women tend to be with lower parity as well. The percentage of women who hadn't given birth before was higher in the MAR than in the SC group (60.3% of the MAR vs. 3/11, 27.3% of SC), as was the percentage of those who had given birth once (27.0% of the MAR vs. 1/11; 9.1% of the SC). Whereas the proportion of those who had given birth more than twice was low in this group (12.7% of the MAR vs. 7/11; 63.6% of the SC).

Regarding history of previous abortion; although the percentage of women with twins and triplets who had history of abortion was low in both groups, it was higher in the SC group of twins (36.0% of SC vs. 27.0% of MAR) as well as among triplet groups (4/11, 36.4% in the SC vs. 19.0% in the MAR).

Regarding the history of multiple births, very similar percentages were found within the two groups of twins, as 12.8% of the MAR group had a personal history of multiple births compared to 12.0% in the SC group. Among triplet groups, the percentage of women who were reported having a personal history of multiple births was slightly higher in the SC group (2/11, 18.2% in SC vs. 7/55, 12.7% in the MAR).

As expected, family history of multiple births was more often found in the SC group of twins (87.0% of the SC vs. 62.1% of the MAR), and triplets (100% of the SC vs. 62.7% of the MAR). The family history of multiple births among twins and triplets, in particular, that after spontaneous conceptions was more often from mothers' side. Furthermore, seven women with spontaneously conceived twin births were reported being part of twins.

Infertility history was not recorded for cases having spontaneously conceived multiple births. Moreover, in this study most couples in the medical assisted conception group had a history of infertility; (141/209, 67.5%) of the couples having twins, (45/55, 81.8%) of those having triplets and all of those having quadruplets. Of the 209 twin neonates in the MAR group, 17 neonates were born after a gender selection procedure, as was the case for 2 of the 59 triplet neonates.

Table 4.5: Medical and obstetrical histories of mothers with multiple births for the SC and MAR groups

Parameters	Twins N=700		Triplets N=74	
	SC N=478	MAR N=222	SC N=11	MAR N=63
<b>Medical history</b>				
	<b>N=478</b>	<b>N=214</b>	<b>N=11</b>	<b>N=57</b>
Yes	33 (6.9%)	23 (10.7%)	1 (9.1%)	3 (5.3%)
No	445 (93.1%)	191 (89.3%)	10 (90.9%)	54 (94.7%)
<b>Cervical stitch</b>				
	<b>N=476</b>	<b>N=214</b>	<b>N=10</b>	<b>N=57</b>
Yes	22 (4.6%)	73 (34.1%)	5 (50.0%)	44 (77.2%)
No	454 (95.4%)	141 (65.9%)	5 (50.0%)	13 (22.8%)
<b>Parity</b>				
	<b>N=478</b>	<b>N=222</b>	<b>N=11</b>	<b>N=63</b>
0	86 (18.0%)	101 (45.5%)	3 (27.3%)	38 (60.3%)
1	78 (16.3%)	51 (23.0%)	1 (9.1%)	17 (27.0%)
≥2	314 (65.7%)	70 (31.5%)	7 (63.6%)	8 (12.7%)
<b>Previous abortion</b>				
	<b>N=478</b>	<b>N=222</b>	<b>N=11</b>	<b>N=63</b>
Yes	172 (36.0%)	60 (27.0%)	4 (36.4%)	12 (19.0%)
No	306 (64.0%)	162 (73.0%)	7 (63.6%)	51 (81.0%)
<b>Previous history of multiple births</b>				
	<b>N=466</b>	<b>N=211</b>	<b>N=11</b>	<b>N=55</b>
Yes	56 (12.0%)	27 (12.8%)	2 (18.2%)	7 (12.7%)
No	410 (88.0%)	184 (87.2%)	9 (81.8%)	48 (87.3%)
<b>Family history of multiple births</b>				
	<b>N=430</b>	<b>N=190</b>	<b>N=11</b>	<b>N=51</b>
Yes	374 (87.0%)	118 (62.1%)	11 (100.0%)	32 (62.7%)
No	56 (13.0%)	72 (37.9%)	—	19 (37.3%)
<b>Infertility history</b>				
		<b>N=209</b>		<b>N=55</b>
Yes	—	141 (67.5%)	—	45 (81.8%)
No	—	68 (32.5%)	—	10 (18.2%)

*Note.*

SC, spontaneous conception; MAR, medical assisted reproduction.

More details on the types of medical diseases among mothers of twins and triplets in (SC and MAR group) will be given in the annex 5.

## 4.4 Description of maternal and obstetrical outcomes of multiple births

### 4.4.1. Description of maternal and obstetrical outcomes of all of the multiple births

Table (4.6) summarizes the complications encountered during the present pregnancy. The analysis revealed that 87.7% of the women with twins and all the women with triplets and quadruplets experienced complications during pregnancy. In the current study, the most common adverse pregnancy outcomes were fetal mal-presentation. Fetal mal-presentation occurred in 68.1% of cases in twin group, among those 40.4% of both twins (breech-breech presentation was the most frequent), 13.3% of the first twin (all except one delivery was breech-cephalic), and 46.3% of the second twin (cephalic-breech was the most frequent) (data was not shown). Data on fetal presentation for triplets and quadruplets was incomplete in the medical records, hence our results should be handled with caution. In addition, the second most common adverse pregnancy outcome was preterm delivery which occurred in 54.2% of the twin births and in all of the triplet and quadruplet cases (mainly after spontaneous onset of labor); these were followed by anemia which occurred in 15.8% of twins, 30.8% of triplets and (2/6, 33.3%), of quadruplets, and PPRM which occurred in 13.6% of twins, 22.2% of triplets, and (2/5, 40.0%) of quadruplets.

Hypertensive complications occurred in (9.3%) of the mothers of twins, (6/75, 6.8%) of triplets and (3/6, 50.0%) of quadruplets (preeclampsia is more likely), and stillbirth 3.3% of twins group, (5/74, 6.8%) of triplets group, and (1/6, 16.7%) of quadruplets. Furthermore, antepartum hemorrhage was found in 5.0% of twins group and (4/74, 5.4%), of triplets group (due mainly to placental problems), but it was not found in quadruplets group, same as for placental complications which were found in 3.0% of the mothers of twins and (3/74, 4.1%) of triplets (abruptio placentae is more common). Intrauterine growth restriction was a complication in 4.4% of twins and for (1/74, 1.4%) of triplets, and other complications 6.4% of the mothers of twins, and (11/74, 14.9%) in triplets. The afore-mentioned complications reported in the twin and triplet group were not recorded for quadruplets. Gestational diabetes mellitus and the twin-to-twin transfusion syndrome were recorded only for twins group; 1.3% had gestational diabetes mellitus, and (5/765, 0.7%) had twin to twin transfusion syndrome.

Regarding delivery, as evident in (Table 4.6), 808 twin births and 89 higher-order multiple births reached potential viability (viability is the potential of the fetus to survive outside the uterus after birth), and mode of delivery was recorded for all twin births except eight births, and for all the higher-order multiple births. The analysis revealed that the cesarean section was the more frequent mode of delivery used by the mothers in all groups of multiple births. Cesarean section was performed for more than half (479/800, 59.9%) of the women with twins and for all except six mothers of higher-order multiples. Of all cases delivered by cesarean section, the majority had emergency cesarean section 74.0% for twins, 70.8% for triplets, and (5/6, 83.3%) for quadruplets.

The most common indications for performing cesarean section in twin groups were fetal mal-presentation 42.8%, previous cesarean section 24.4%, obstetrical indications 15.8%, fetal indication 8.4%, maternal indications 3.1%, and mother's request 2.6%. For the

higher-order multiples, the indication for cesarean section was higher-order multiple pregnancy, among which the majority of women were in labor. Cesarean section conducted without medical indications were categorized under “other indications”, this constituted 18.2% of twin deliveries and (6/60, 10.0%) of triplets and one of the six (16.7%) of quadruplets (data not shown).

Vaginal delivery had to be performed for 39.5% of the mothers of twins as for (6/82, 7.3%) of triplets. Spontaneous vaginal delivery was the mode for the majority of cases, whereas instrumental vaginal delivery was the mode for only (9/316, 2.8%) of cases in the twin group. For(5/800, 0.6%) of mothers in the twin group, there was a combined mode of delivery (the first twin was born vaginally, while the second by cesarean section).

Postpartum hemorrhage occurred for 6.0% of the women with twins, (9/74, 12.0%) of the women with triplets, and for two of the six (33.0%) of quadruplets. It is worth mentioning that the majority of those mothers who suffered from postpartum hemorrhage were found in public hospitals. In the current study, there was no maternal mortality in any of the studied births.

Table 4.6: Maternal and obstetrical outcomes of all of the multiple birth groups

Complications	Multiple births N=896	
	Twins N=808	Triplets and quadruplets N=88
Preterm delivery	438/808 (54.2%)	88/88 (100.0%)
Antepartum hemorrhage	38/765 (5.0%)	4/80 (5.0%)
PPROM	98/723 (13.6%)	22/71 (30.9%)
Hypertensive complications ††	71/765 (9.3%)	8/80 (10.0%)
Placental complications ‡	23/765 (3.0%)	3/80 (3.8%)
Gestational diabetes mellitus	10/765 (1.3%)	—
Anemia*	116/736 (15.8%)	18/77 (23.4%)
Other complications §	49/765 (6.4%)	11/80 (13.8%)
Fetal mal-presentation	497/730 (68.1%)	28/ 34 (82.4%)
Intrauterine growth restriction	34/765 (4.4%)	1/80 (1.3%)
Stillbirth	23/765 (3.3%)	6/80 (7.5%)
Twin to Twin Transfusion syndrome	5/765 (0.7%)	—
<b>Mode of delivery</b>		
	<b>N=800</b>	<b>N=88</b>
Vaginal	316 (39.5%)	6 (6.8%)
Spontaneous	307 (97.2%)	6 (100.0%)
Instrumental	9 (2.8%)	—
Caesarean section	479 (59.9%)	82 (93.1%)
Elective	114/438 (26.0%)	20/71 (28.2%)
Emergency	324/438 (74.0%)	51/71 (71.8%)
Mixed	5 (0.6%)	—
Postpartum hemorrhage	50/759 (6.6%)	11/80 (13.8%)

*Note.*

PPROM: preterm premature rupture of membrane.

† Included preeclampsia, pregnancy-induced hypertension, and HELLP syndrome (please refer to annex 6).

‡ Included abruption placenta, and placenta previa (please refer to annex 7).

\*Anemia: Haemoglobin <10.5g/dl at the time of admission for delivery.

§Includes unspecified kidney problems, DVT, polyhydramnios, oligohydramnios, thrombocytopenia, hydronephrosis, placental calcification, chorioamnionitis, generalized edema, pancreatitis, cholecystitis, cholestasis, varicose vein, unspecified liver problems, history of preterm labor, chest and back pain, and unspecified abdominal pain, pyelonephritis, and suspected coagulopathy (please refer to annex 8).

#### **4.4.2. Description of maternal and obstetrical outcomes according to the method of conception (SC, MAR).**

Table (4.7) summarizes the complications encountered by the women with multiple births in both groups (spontaneous conception and MAR). The comparisons between the groups were limited to twins and triplets. The analysis revealed that, the majority of the women having twins in both groups had adverse pregnancy outcomes (87.9% of the SC vs. 86.0% of the MAR), the difference was small. All women having triplets in both groups had adverse pregnancy outcomes. Among twin groups, the prevalence of fetal mal-presentation was equally common in both groups (68.1% of the MAR vs. 67.2% of the SC). Although more than half of the women in both groups had preterm delivery, the percentage was higher for women in the MAR group (61.7% of the MAR vs. 51.5% of the SC group).

There was a slightly higher percentage of PPRM in the MAR group than in the SC group (16.9% of the MAR vs. 12.0% of the SC), as it was for hypertensive complications (11.2% of the MAR vs. 7.5% of the SC), antepartum hemorrhage percentage was (8.4 % of the MAR vs. 3.8% of the SC), placental complications (4.2% of the MAR vs. 2.5% of the SC), intrauterine growth restriction (5.2% of the SC vs. 4.2% of the MAR group), whereas the incidence of anemia was slightly lower in the MAR group (13.5% of the MAR vs. 17.1% of the SC group). Very similar results were obtained in the prevalence of other pregnancy complications (6.7% of the MAR vs. 6.1% of the SC group), stillbirth (2.7% of the SC vs. 5/215, 2.3% of the MAR group), Gestational diabetes (4/215, 1.9% of the MAR group vs. 5/477, 1.0% of the SC) and Twin to Twin Transfusion Syndrome (4/477, 0.8% of the SC vs. 1/215, 0.5% of the MAR group).

Data concerning maternal and obstetrical complications encountered by the women with triplets are also shown in (Table 4.7). All the triplet pregnancies in both groups ended preterm. A higher percentage of hypertensive complications was observed among triplets resulting in the SC group as compared to MAR group (2/11, 18.2% of the SC vs. 3/58, 5.2% of the MAR), as well as for anemia (4/11, 36.4% of the SC vs. 19.6% of the MAR group). The percentage of other pregnancy complications was slightly higher in the SC group compared to the MAR group (2/11, 18.2% of SC vs. 9/58, 15.5%), as well as for stillbirth (1/11, 9.1% of SC vs. 3/58, 5.2% of MAR), and placental complications (1/11, 9.1% of SC vs. 2/58, 3.4% of MAR). However, the occurrence of PPRM was slightly lower in the SC group (3/11, 27.3% of the SC vs. 32.0% of the MAR). In the MAR group only, the following cases were recorded: four cases of antepartum hemorrhage, and one case of intrauterine growth restriction. No cases of gestational diabetes mellitus and twin to twin transfusion syndrome occurred in both groups of triplets.

Regarding the mode of delivery, women with twins in the MAR group underwent cesarean deliveries more frequently than the women in the SC group (78.3% of the MAR group vs. 52.2% of the SC group). All the women with triplets in the SC group and all except two women in the MAR group were delivered by cesarean section. Although most of the cesarean deliveries in both groups of multiple births were an emergency procedure, the

percentage was higher in the SC group among twins (78.1% of the SC vs. 66.9% of the MAR) and triplets (9/10, 90.0% of the SC vs. 66.0% of triplets), whereas the percentage of elective cesarean section was lower in the SC group among twins (21.9% of the SC vs. 33.1% of the MAR group) and triplets (1/10, 10.0% of the SC vs. 34.0% of the MAR). Cesarean section indications were slightly different in both groups of twins, except other indications (Cesarean section conducted without medical indications), where the percentage was higher in the MAR group.

Vaginal delivery was performed more frequently for the women with twins in the SC group (47.2% of the SC vs. 21.3% of the MAR). Among triplets, only two of the 63 (3.2%) women with triplets in the MAR group delivered vaginally. The percentage of combined delivery was not different between the two groups of twins (3/477, 0.6% in the SC vs. 1/221, 0.5% in the MAR group). The prevalence of postpartum hemorrhage in the SC group 7.1% was very similar compared with the prevalence in the MAR group 6.5%. Among triplet groups, the prevalence of postpartum hemorrhage appeared to be slightly higher in the SC group (2/11, 18.2% of the SC vs. 6/58, 10.3% of the MAR).

**Table 4.7 -A: Maternal and obstetrical outcomes for the SC and MAR groups**

Complication	Twins N=700		Triplets N=74	
	SC N=478	MAR N=222	SC N=11	MAR N=63
<b>Maternal and obstetrical complications</b>				
Preterm delivery	246/478 (51.5%)	137/ 222 (61.7%)	11/11 (100.0%)	63/63 (100.0%)
Antepartum hemorrhage	18/477 (3.8%)	18/215 (8.4%)	—	4/58 (6.9%)
Hypertensive complications	36/477 (7.5%)	24/215 (11.2%)	2/11 (18.2%)	3/58 (5.2%)
Placental complications	12/477 (2.5%)	9/215 (4.2%)	1/11 (9.1%)	2/58 (3.4%)
PPROM	55/459 (12.0%)	34/201 (16.9%)	3/11 (27.3%)	16/ 50 (32.0%)
Gestational diabetes mellitus	5/477 (1.0%)	4/215 (1.9%)	—	—
Anemia	78/456 (17.1%)	28/208 (13.5%)	4/11 (36.4%)	11/ 56 (19.6%)
Other complications	29/477 (6.1%)	15/215 (7.0%)	2 (18.2%)	9/58 (15.5%)
Fetal mal-presentation	310/461 (67.2%)	128/188 (68.1%)	6/7 (85.7%)	18/23 (78.3%)
Intrauterine growth restriction	25/477 (5.2%)	9/215 (4.2%)	—	1/58 (1.7%)
Still birth	13/477 (2.7%)	5/215 (2.3%)	1/11 (9.1%)	3/58 (5.2%)
Twin to Twin Transfusion syndrome	4/477 (0.8%)	1/215 (0.5%)	—	—

**Table 4.7 -B: Maternal and obstetrical outcomes for the SC and MAR groups**

Mode of delivery				
	N=477	N=221	N=11	N=63
Vaginal	225 (47.2%)	47 (21.3%)	—	2 (3.2%)
Spontaneous	220 (97.8%)	44 (93.6%)	—	2 (100.0%)
Instrumental	5 (2.2%)	3 (6.4%)	—	—
Caesarean section	249 (52.2%)	173 (78.3%)	11 (100.0%)	61 (96.8%)
Elective	54/247 (21.9%)	53/160 (33.1)	1/10 (10.0%)	18/53 (34.0%)
Emergency	193/247 (78.1%)	107/160 (66.9%)	9/10 (90.0%)	35/53 (66.0%)
Mixed	3 (0.6%)	1 (0.5%)	—	—
Postpartum hemorrhage	34/478 (7.1%)	14/215 (6.5%)	2/11(18.2%)	6/58 (10.3%)

*Note.*

SC, Spontaneous conception; MAR: medical assisted reproduction; PPROM, preterm premature rupture of membrane. More details on the types of placental complications, hypertensive diseases and other complications for the overall groups of multiple births and according to method of conception will be given in the annex 6, 7 and 8.

#### **4.5 Description of maternal characteristics and obstetrical results according to the type of MAR (IVF, IUI and IOO)**

In the current study, maternal characteristics and obstetrical results of both twins and triplet groups were assessed according to the type of MAR (IVF, IUI, and IOO) (Table 4.8, 4.9, and 4.10). Among twin groups, the IUI-treated women were more likely than those in other groups to have higher education (4/7, 57.1% of the IUI vs. 39.8% of the IVF vs. 33.3% of the IOO), to be employed (4/7, 57.1% of the IUI vs. 16.2% of the IVF vs. 9.8% of the IOO), and to report living in the middle of the WB (5/9, 55.6% of the IUI vs. 34.9% of the IVF vs. 24.5% of the IOO). The IOO-treated women were more likely than women in other groups to report living in south of the WB (40.2% of the IOO vs. 24.8% of the IVF vs. 1/9, 11.1% of the IUI), to deliver in public hospitals (76.5% of the IOO vs. 51.4% of the IVF vs. 3/9, 33.3% of the IUI group), to have given birth more than twice (57.8% of the IOO vs. 3 of the 9; 33.3% of the IUI vs. 6.4% of the IVF). Besides, they were less likely to have infertility (36.3% in IOO vs. 71.4% in IUI vs. 99.0% in IVF), and less underwent a cervical stitch (16.7% in IOO vs. 37.5% in IUI vs. 51.0% in IVF). Among the IVF women the history of abortion was less common compared with those in other groups (21.1% of the IVF vs. 33.3% of the IUI vs. 33.3% of the IOO).

Among triplet groups, the IOO treatment was associated with younger maternal ages (mean 23.7, SD 2.9 vs. 25.2, SD 5.1 of the IUI vs. 28.4, SD 4.6 of the IVF group), had a higher rate of consanguineous marriage (5/9, 55.6% of the IOO vs. 1/5, 20.0% of the IUI vs. 7/38, 18.4% of the IVF), more frequent deliveries in public hospitals (7/11, 63.6% of the IOO vs. 3/6; 50.0% of the IUI vs. 39.1% of the IVF), and reflected less infertility (2/9, 22.2% of the IOO vs. 4/5, 80.0% of the IUI vs. 95.1% of the IVF). The IUI-treated women were more likely to report living in the north of the WB (5/6, 83.3% of the IUI vs. 54.3% of the IVF vs. 5/11, 45.4% of the IOO), and there were more women who didn't give birth previously (5/6, 83.3% of the IUI vs. 58.7% of the IVF vs. 6/11, 54.5% of the IOO). In the

IVF group there were more women who received a cervical stitch than in other groups (82.9% of the IVF vs. 7/11, 63.6% of the IOO vs. 3/5, 60.0% of the IUI group).

Regarding pregnancy complications, for women with twins, the IOO-treated women were less likely to have complications by preterm delivery, (52.9% in IOO vs. 67.9% in IVF vs. 77.8% in IUI group) and to have delivery by cesarean section (58.8% of IOO vs. 88.9% of IUI vs. 95.4% of IVF). In the IUI group the women were more likely than those in other groups to have hypertensive complications (3/8, 37.5% of the IUI vs. 14.3% of the IVF vs. 5.9% of the IOO group), but they were less likely to have fetal mal-presentation (4/8, 50.0% of IUI vs. 66.7% of the IOO vs. 71.4% of the IVF). For triplets, the IOO-treated women were less likely to have anemia during pregnancy (1/11, 9.1% of the IOO vs. 1/5, 20.0% of the IUI vs. 9/40, 22.5% of the IVF group). Women in the IUI group were more likely than women in other groups to experience PPRM (3/5, 60.0% of the IUI vs. 31.4% of the IVF vs. 2/10, 20.0% of the IOO group).

When pregnancy complications were stratified by the women's age and parity, women with twins aged less than 30 years were more likely than women aged more than 30 years to develop preterm delivery. Women with twins who had not given birth before were also more likely than women who had given birth once and twice to have preterm delivery. The incidence of preterm delivery was found higher in the MAR groups even after stratification according to mothers' age and parity. Furthermore, hypertensive disorders appeared to be higher among women with twins aged >30 years, fetal mal-presentation also appeared to be higher with increasing age. The incidence of PPRM appeared slightly higher among women with twins who had not given birth before. The other assessed complications were independent of the mother's age and parity. Among triplets, the assessed complications were independent of the mothers' age and parity except for the incidence of PPRM, in which the incidence appeared slightly higher among women who had not given birth before.

Table 4.8: Socio-demographic characteristics of the multiple birth mothers according to the type of MAR (IVF, IUI and IOO)

Parameters	Twins N=220			Triplets N=63		
	IVF N=109	IUI N=9	IOO N=102	IVF N=46	IUI N=6	IOO N=11
<b>Maternal age (years)</b>	<b>N=109</b>	<b>N=9</b>	<b>N=102</b>	<b>N=46</b>	<b>N=6</b>	<b>N=11</b>
Mean (SD)	28.1 (4.3)	28.0 (4.2)	27.5 (4.9)	28.4 (4.6)	25.2 (5.1)	23.7 (2.9)
Range(minimum-maximum)	17-39	23-33	18-39	19-39	19-32	20-29
<20	2 (1.8%)	—	6 (5.9%)	1 (2.2%)	1 (16.7%)	—
20-24	21 (19.3%)	2 (22.2%)	25 (24.5%)	8 (17.4%)	2 (33.3%)	7 (63.6%)
25-29	48 (44.0%)	3 (33.3%)	35 (34.3%)	22 (47.8%)	1 (16.7%)	4 (36.4%)
30-34	30 (27.5%)	4 (44.4%)	27 (26.5%)	9 (19.6%)	2 (33.3%)	—
35-39	8 (7.3%)	—	9 (8.8%)	6 (13.0%)	—	—
40-45	—	—	—	—	—	—
<b>Mother's education</b>	<b>N=93</b>	<b>N=7</b>	<b>N=102</b>	<b>N=38</b>	<b>N=5</b>	<b>N=9</b>
Basic	28 (30.1%)	—	30 (29.4%)	8 (21.0%)	1 (20.0%)	2 (22.2%)
Secondary	28 (30.1%)	3 (42.9)	38 (37.3%)	12 (31.6%)	—	3 (33.3%)
Higher	37 (39.8%)	4 (57.1%)	34 (33.3%)	18 (47.4%)	4 (80.0%)	4 (44.4%)
<b>Mother's work status</b>	<b>N=99</b>	<b>N=7</b>	<b>N=99</b>	<b>N=39</b>	<b>N=5</b>	<b>N=10</b>
House wife	81 (81.8%)	3 (42.9%)	89 (87.3%)	29 (74.3%)	4 (80.0%)	9 (90.0%)
Employed	16 (16.2%)	4 (57.1%)	10 (9.8%)	9 (23.1%)	—	1 (10.0%)
Student	2 (2.0%)	—	3 (2.9%)	1 (2.6%)	1 (20.0%)	—
<b>Consanguinity</b>	<b>N=86</b>	<b>N=7</b>	<b>N=100</b>	<b>N=38</b>	<b>N=5</b>	<b>N=9</b>
Relative	19 (22.1%)	2 (28.6%)	33 (33.0%)	7 (18.4%)	1 (20.0%)	5 (55.6%)
Not relative	67 (77.9%)	5 (71.4%)	67 (67.0%)	31 (81.6%)	4 (80.0%)	4 (44.4%)
<b>Place of residence (WB)</b>	<b>N=109</b>	<b>N=9</b>	<b>N=102</b>	<b>N=46</b>	<b>N=6</b>	<b>N=11</b>
South	27 (24.8%)	1 (11.1%)	41 (40.2%)	14 (30.4%)	—	3 (27.3%)
Center	38 (34.9%)	5 (55.6%)	25 (24.5%)	7 (15.2%)	1 (16.7%)	3 (27.3%)
North	44 (40.3%)	3 (33.3%)	36 (35.3%)	25 (54.3%)	5 (83.3%)	5 (45.4%)
<b>Type of hospital</b>	<b>N=109</b>	<b>N=9</b>	<b>N=102</b>	<b>N=46</b>	<b>N=6</b>	<b>N=11</b>
Public	56 (51.4%)	3 (33.3%)	78 (76.5%)	18 (39.1%)	3 (50.0%)	7 (63.6%)
Private	53 (48.6%)	6 (66.7%)	24 (23.5%)	28 (60.9%)	3 (50.0%)	4 (36.4%)

Note.

IVF, In vitro fertilization; IUI, intrauterine insemination; IOO, Induction of ovulation; SD, standard deviation; WB, West Bank.

Table 4.9: Medical and obstetrical history of the multiple birth mothers according to the type of MAR (IVF, IUI and IOO)

Parameters	Twins N=220			Triplets N=63		
	IVF N=109	IUI N=8	IOO N=102	IVF N=46	IUI N=6	IOO N=11
<b>Medical history</b>	<b>N=104</b>	<b>N=8</b>	<b>N=102</b>	<b>N=41</b>	<b>N=5</b>	<b>N=11</b>
Yes	11 (10.6%)	1 (12.5%)	11 (10.8%)	2 (4.9%)	—	1 (9.1%)
No	93 (89.4%)	7 (87.5%)	91 (89.2%)	39 (95.1%)	5 (100.0%)	10 (90.9%)
<b>Cervical stitch</b>	<b>N=104</b>	<b>N=8</b>	<b>N=102</b>	<b>N=41</b>	<b>N=5</b>	<b>N=11</b>
Yes	53 (51.0%)	3 (37.5%)	17 (16.7%)	34 (82.9%)	3 (60.0%)	7 (63.6%)
No	51 (49.0%)	5 (62.5%)	85 (83.3%)	7 (17.1%)	2 (40.0%)	4 (36.4%)
<b>Parity</b>	<b>N=109</b>	<b>N=9</b>	<b>N=102</b>	<b>N=46</b>	<b>N=6</b>	<b>N=11</b>
0	70 (64.2%)	3 (33.3%)	27 (26.5%)	27 (58.7%)	5 (83.3%)	6 (54.5%)
1	32 (29.4%)	3 (33.3%)	16 (15.7%)	14 (30.4%)	—	3 (27.3%)
≥2	7 (6.4%)	3 (33.3%)	59 (57.8%)	5 (10.9%)	1 (16.7%)	2 (18.2%)
<b>Previous abortion</b>	<b>N=109</b>	<b>N=9</b>	<b>N=102</b>	<b>N=46</b>	<b>N=6</b>	<b>N=11</b>
Yes	23 (21.1%)	3 (33.3%)	34 (33.3%)	9 (19.6%)	—	3 (27.3%)
No	86 (78.9%)	6 (66.7%)	68 (66.7%)	37 (80.4%)	6 (100.0%)	8 (72.7%)
<b>Previous history of multiple births</b>	<b>N=102</b>	<b>N=8</b>	<b>N=101</b>	<b>N=40</b>	<b>N=5</b>	<b>N=10</b>
Yes	9 (8.8%)	1 (12.5%)	17 (16.8%)	7 (17.5%)	—	—
No	93 (91.2%)	7 (87.5%)	84 (83.2%)	33 (82.5%)	5 (100.0%)	10 (100.0%)
<b>Family history of multiple births</b>	<b>N=83</b>	<b>N=7</b>	<b>N=100</b>	<b>N=37</b>	<b>N=5</b>	<b>N=9</b>
Yes	42 (50.6%)	6 (85.7%)	70 (70.0%)	24 (64.9%)	2 (40.0%)	6 (66.7%)
No	41 (49.4%)	1 (14.3%)	30 (30.0%)	13 (35.1%)	3 (60.0%)	3 (33.3%)
<b>Infertility history</b>	<b>N=99</b>	<b>N=7</b>	<b>N=102</b>	<b>N=41</b>	<b>N=5</b>	<b>N=9</b>
Yes	98 (99.0%)	5 (71.4%)	37 (36.3%)	39 (95.1%)	4 (80.0%)	2 (22.2%)
No	1 (1.0%)	2 (28.6%)	65 (63.7%)	2 (4.9%)	1 (20.0%)	7 (77.8%)

Note.

IVF, In vitro fertilization; IUI, intrauterine insemination; IOO, Induction of ovulation.

More details on the types of medical diseases for the women of multiple births dispersed according to the type of MAR will be given in the annex 5.

Table 4.10: Maternal and obstetrical outcomes according to the type of MAR (IVF, IUI and IOO)

Parameters	Twins N=220			Triplets N=63		
	IVF N=109	IUI N=8	IOO N=102	IVF N=46	IUI N=6	IOO N=11
<b>Maternal and obstetrical complications</b>						
Preterm delivery	74/109 (67.9%)	7/9 (77.8%)	54/102 (52.9%)	46 (100.0%)	6 (100.0%)	11 (100.0%)
Antepartum hemorrhage	8 (7.6%)	—	10 (9.8%)	3 (7.1%)	—	1 (9.1%)
Hypertensive complications	15 (14.3%)	3 (37.5%)	6 (5.9%)	2 (4.8%)	—	1 (9.1%)
Placental complications	3 (2.9%)	—	6 (5.9%)	—	—	2 (18.2%)
PPROM	20/98 (20.4%)	1/8 (12.5%)	13/95 (13.7%)	11/35 (31.4%)	3/5 (60.0%)	2/10 (20.0%)
Gestational Diabetes mellitus	—	—	4 (3.9%)	—	—	—
Anemia	13/101 (12.9%)	1/8 (12.5%)	14/99 (14.1%)	9/40 (22.5%)	1/5 (20.0%)	1/11 (9.1%)
Other complications	9 (8.6%)	1 (12.5%)	5 (4.9%)	6 (14.3%)	1 (20.0%)	2 (18.2%)
Fetal mal-presentation	60/84 (71.4%)	4/8 (50.0%)	64/96 (66.7%)	15/16 (93.8%)	1/1 (100.0%)	2/6 (33.3%)
Intrauterine growth restriction	7 (6.7%)	—	2 (2.0%)	1 (2.4%)	—	—
Still birth	2 (1.9%)	—	3 (2.9%)	2 (4.8%)	—	1 (9.1%)
Twin to twin transfusion syndrome	—	—	1 (1.0%)	—	—	—
<b>Mode of delivery</b>						
	<b>N=108</b>	<b>N=9</b>	<b>N=101</b>	<b>N=46</b>	<b>N=6</b>	<b>N=11</b>
Vaginal	5 (4.6%)	1 (11.1%)	41 (40.2%)	1 (2.2%)	—	1 (9.1%)
Spontaneous	4 (80.0%)	1 (100.0%)	39 (95.1%)	1 (100.0%)	—	1 (100.0%)
Instrumental	1 (20.0%)	—	2 (4.9%)	—	—	—
Caesarean section	103 (95.4%)	8 (88.9%)	60 (58.8%)	45 (97.8%)	6 (100.0%)	10 (90.9%)
Elective	32/96 (33.3%)	2/7 (28.6%)	19/57 (33.3%)	14/40 (35.0%)	2/5 (40.0%)	2/8 (25.0%)
Emergency	64/96 (66.7%)	5/7 (71.4%)	38/57 (66.7%)	26/40 (65.0%)	3/5 (60.0%)	6/8 (75.0%)
Postpartum hemorrhage	7/105 (6.7%)	—	7/102 (6.9%)	2 (4.2%)	—	—

*Note.*

IVF, In vitro fertilization; IUI, intrauterine insemination; IOO, Induction of ovulation, PPRM; preterm premature rupture of membrane.

More details on the types of placental complications, hypertensive diseases and the other pregnancy complications dispersed according to the type of MAR will be given in the annex 6, 7 and 8.

## 4.6 Neonatal outcomes of multiple births

### 4.6.1. Characteristics of neonates for the whole multiple birth groups

This section of the study focused on the neonatal outcomes including (gestational age, birth weight, birth weight discordance, gender, sex concordance, and Apgar score at 1 and 5 minutes). Neonatal outcomes in terms of morbidity and mortality were described as well.

As shown in (Figure 4.2), 46.6% of twin neonates were delivered at 32-36 weeks, the other large group 46.2% of neonates were delivered at  $\geq 37$  weeks, the lowest percentage (7.2%) was for neonates born less than 32 weeks. The lowest gestational age for twins was 24 weeks and the highest gestational age was 42.4 weeks, with six neonates found with late term (41 0/7 weeks) and one neonate was postdate (42 weeks and above) of delivery. All of the triplets and quadruplets neonates were delivered prematurely at ( $<37$  weeks) of gestation. Most of the triplet neonates (159/239, 66.5%) and quadruplet neonates (15/23, 65.2%) were delivered between 32 to 36 weeks. Among the triplets group, the lowest gestational age was 25 weeks, and the highest was 36 weeks, in this group six neonates reached 35 weeks and seven reached 36 weeks. Among the quadruplets group, the lowest gestational age was 31 weeks, and the highest was 33 weeks. The mean gestational age of twins at delivery was (36.0 weeks, SD 2.9), for triplets (32.2 weeks, SD 2.8), and for quadruplets (32.0 weeks, SD 0.9).

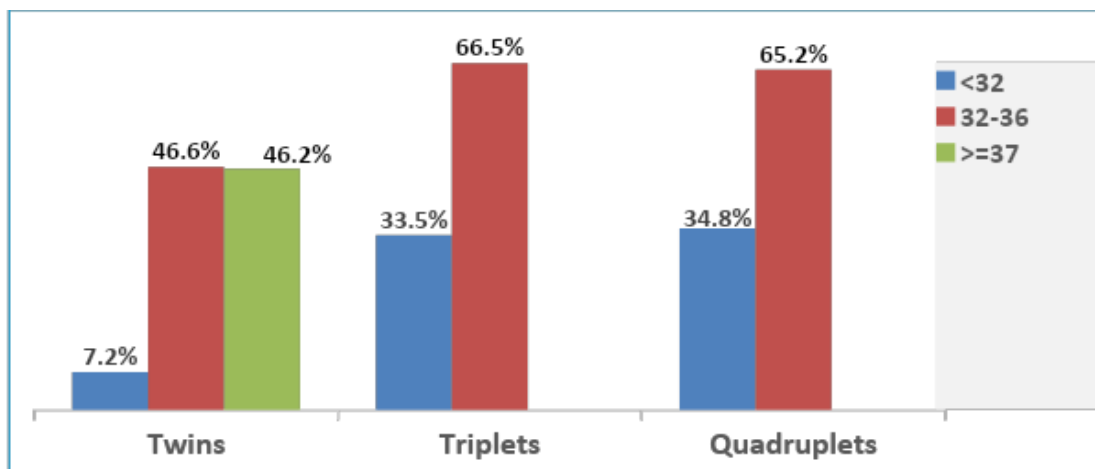


Figure 4.2: The percentage distribution of gestational age (in weeks) for multiple births at delivery

Figure (4.3) shows the birth weight of multiple neonates. As clear in the figure 46.9% of twin neonates had birth weight between 1,500g to less than 2,500g, the other large group 46.0% had birth weight equal to or more than 2,500g, while the lowest percentage (7.1%) was for the neonates with birth weight less than 1,500g. The lowest birth weight was 400g with gestational age of 24 weeks for one case only, whereas the highest birth weight was 4,800g which was for one case as well, where the mother experienced gestational diabetes. All except seven triplet neonates had birth weights less than 2,500g. The majority (147/238, 61.8%) had a birth weight between 1,500 to 2,500g. The minimum birth weight was 300g, which was one case only delivered at 27 weeks of gestation; and the maximum

birth weight was 3000g, which was one case only delivered at 35.7 weeks of gestation. All of the quadruplet neonates had birth weights less than 2,500g. About half of them 52.2% (12/23) had birth weight less than 1,500g and 47.8% had birth weight between 1,500g to 2,500 g. The minimum birth weight was 1,040g; and the maximum was 1,950g. The mean birth weight of twins was (2370.3g, SD 584.5), triplets (1608.5g, SD 476.9), and quadruplets (1480.1g, SD 242.4). The analysis of birth weight by birth order for twins and triplet groups showed no difference (data not shown).

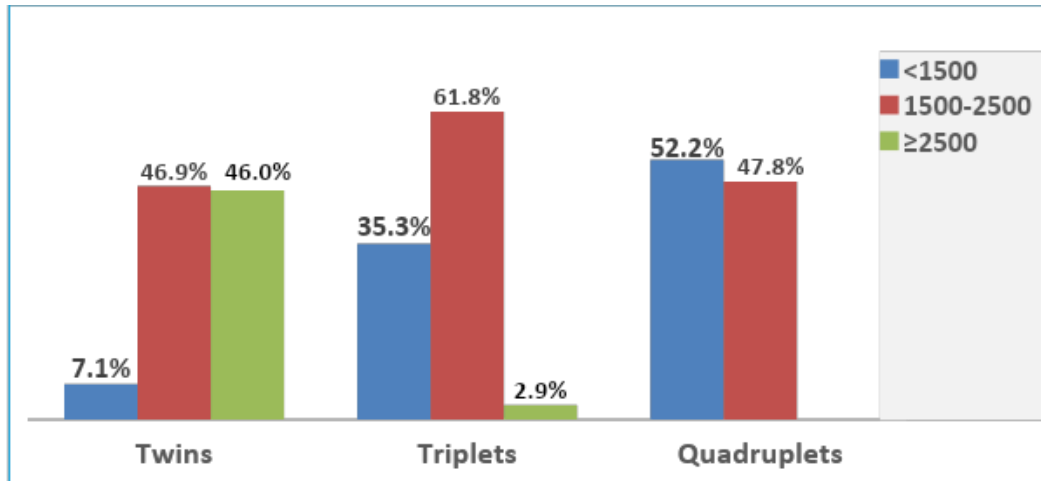


Figure 4.3: The percentage distribution of birth weight (in grams) for multiple births at delivery

As regards to birth weight discordance, it was found that the majority (551/779, 70.7%) of twin neonates were found with concordant birth weight (discordance less than 15%), mild birth weight discordance (15-24.9%) was found in 19.3%. In addition, in 9.9% birth weight discordance was severe ( $\geq 25\%$ ). Birth weight discordance was also calculated for triplets and quadruplets. The researcher compared the heaviest and the lightest triplets and quadruplets and found that 44.7% of the triplets were found with concordant birth weight (discordance less than 15%). In 23.7% of triplets, birth weight discordance was mild between 15 to 24.9%, and in 31.6% the discordance was severe ( $\geq 25\%$ ). Of the five quadruplet sets, 2 sets (40.0%) were found with concordant birth weight (discordance  $< 15\%$ ), and 3 sets (60.0%) birth weight discordance was ( $\geq 25\%$ ). A total overview of the birth weight discordance distribution for triplets and quadruplets will be given in the annex 10.

Figure (4.4) depicts the distribution of neonates' gender. About half of twin neonates (51.5%) were males and 48.5% were females, and about half of triplet neonates (51.0%) were females and 49.0% were males. Among quadruplets, male neonates predominated (14/23, 60.9%) versus (9/23, 39.1%) females. In a review of the prior studies, there appears to have been no mention of male domination in the case of quadruplets' pregnancies, so the possible reason for this is our limited population size.

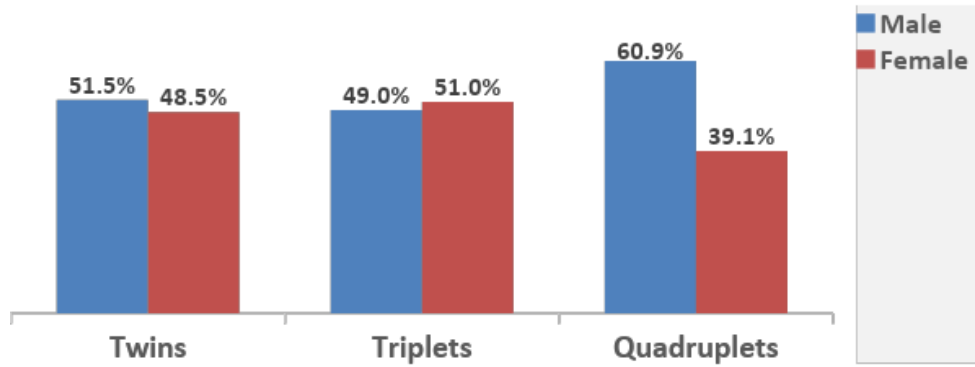


Figure 4.4: The percentage distribution of the multiple birth neonates' gender

It is apparent from (Figure. 4.5) that most of twin births (484/779, 62.1%) were the same sex, 37.9% of neonates were a different sex, whereas most of triplet births (60/77, 77.9%) were a different sex and only 22.1% were the same sex. All of the neonates of quadruplets were different sex. Among those who were the same sex, 51.9% of twins were all males, and 48.1% were all females. Among 17 triplet births, 10 (58.8%) were all females and 7 (41.2%) were all males (data was not shown).

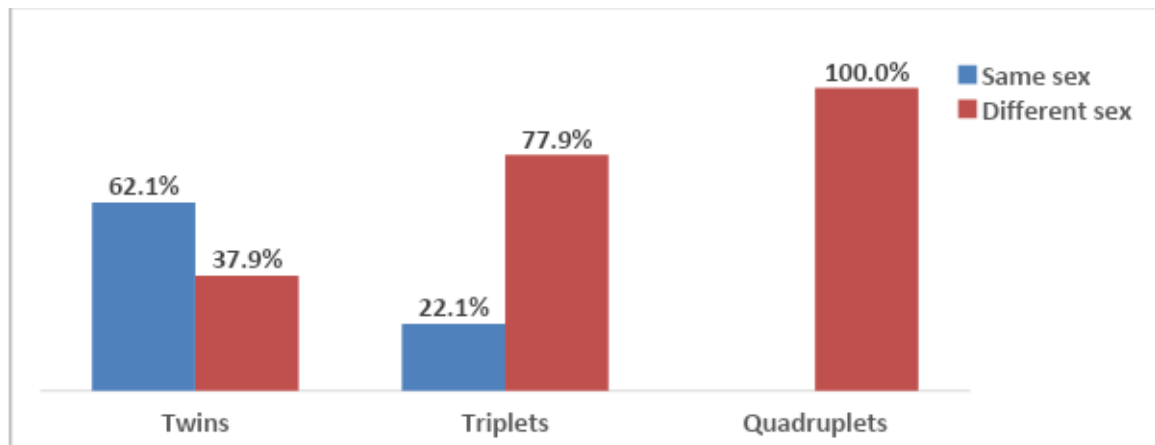


Figure 4.5: The percentage distribution of the sex concordance of multiple births neonates

As can be seen in (Figure 4.6), most of the twin neonates (1338/1567, 85.4%) had Apgar score  $\geq 7$  at one minute of delivery. On the contrary, the neonates of triplets and quadruplets as most of the triplets (137/233, 58.8%) and quadruplets (15/23, 65.2%) had Apgar score  $< 7$  at one minute of delivery.

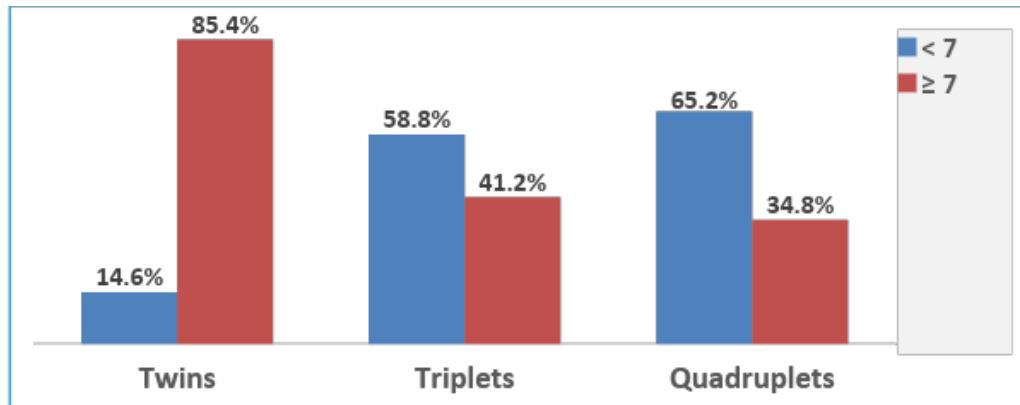


Figure 4.6: The percentage distribution of the one-minute Apgar score among multiple births

The result of Apgar score at 5 minutes of delivery can be seen in (Figure 4.7). The majority of twins (1466/1534, 95.6%), triplets (195/233, 83.7%), and quadruplets (21/23, 91.3%) had Apgar score  $\geq 7$ .

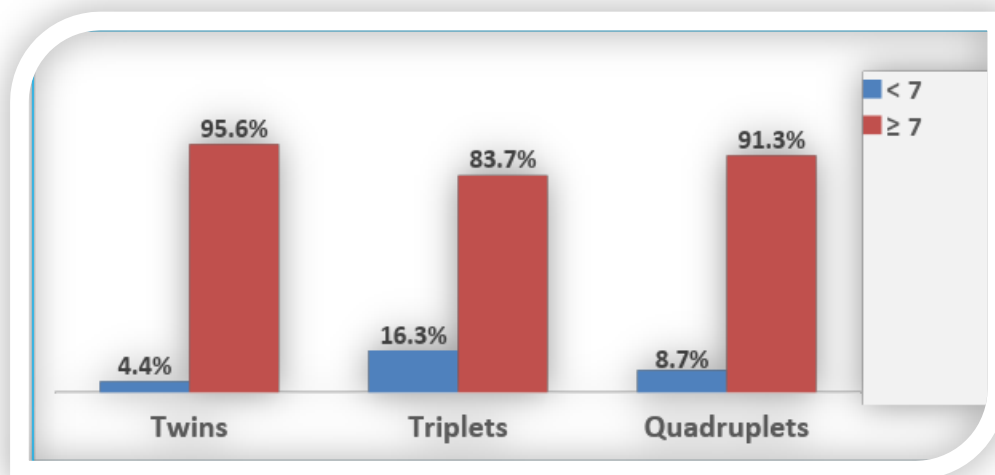


Figure 4.7: The percentage distribution of the five-minute Apgar score among multiple births

#### 4.6.2. Characteristics of the multiple birth neonates according to the method of conception (spontaneous, MAR)

Table (4.11) displays the characteristics of the multiple birth neonates of both groups (SC and MAR). Comparisons were limited to twins and triplets. Twin babies conceived through medically assisted treatment were born at lower gestational age (mean 35.4 weeks, SD 2.7, minimum=25; maximum=40) than those conceived spontaneously (mean 36.1 weeks, SD 2.9, minimum=24; maximum=42.4). In addition, there were more neonates born between 32-36 weeks in the MAR group (54.0% in MAR vs. 43.7% in SC), and less neonates born  $\geq 37$  weeks in this group (38.3% in the MAR group vs. 49.0% in the SC). The percentage

of twin neonates born <32 weeks was very close between the two groups (7.7% in the MAR vs. 7.2% in the SC).

All triplet pregnancies ended preterm. Mean gestational age at delivery was similar between the two groups (32.5 weeks, SD 2.8, minimum=28; maximum=36 in the SC group vs. 32.3 weeks, SD 2.6, minimum=25; maximum=36 in the MAR group), but the distribution of neonates born between 32-36 weeks was higher in the MAR group (72.3% of the MAR vs. 56.3% of the SC group), whereas the distribution of those born <32 weeks was lower in this group (27.7% of the MAR vs. 43.7% of the SC).

The average birth weight among twin groups was found to be slightly lower in those conceived by medically assisted treatments (around 127g lighter) (2275.6g, SD 614.7, minimum=590; maximum=4,800) as compared to those conceived spontaneously (2402.6 g, SD 582.2, minimum=400; maximum=3,950), but there were more neonates weighing between 1,500 to 2,500 g in the MAR group (52.0% of the MAR vs. 44.4% of the SC), and less neonates weighing  $\geq 2,500$  g in this group (37.6% of the MAR vs. 49.4% of the SC). The distribution of neonates weighing <1,500 g varied slightly between groups with higher distribution in the MAR group (10.4% of the MAR vs. 6.2% of the SC).

Twin neonates in both groups mostly had concordant birth weight (discordance <15%), (71.3% of the SC vs. 69.2% of the MAR), mild birth weight discordance (15 to 24.9%) was found in (20.5% of MAR vs. 18.8% of the SC). Small differences were found. Severe birth weight discordance of  $\geq 25\%$  was equally less frequent in both groups (10.3% of the MAR vs. 9.9% of the SC) (please refer to annex 11).

All triplet neonates in both groups except seven in the medical assisted conception group had birth weight <2,500g. The mean birth weight in the MAR group was slightly lower (an average of 85.6g) than the mean in the SC group (1618.9g, SD 466.2, minimum=300; maximum=3,000) vs. 1704.5g, SD 426.6, minimum=850; maximum=2,400 in the SC). The distribution of birth weight varies slightly between the two groups with higher distribution of neonates weighed between 1,500 to 2,500g in the SC group (22/32, 68.7% of the SC vs. 115/184, 62.5% in the MAR), and lower distribution of neonates weighed <1,500g in this group (31.3% of the SC vs. 33.7% of the MAR).

The researcher compared the heaviest and the lightest triplets and found that the rate of neonates with birth weight discordance of <15% was more frequent among spontaneously conceived neonates than among medically assisted conceived neonates (6/10, 60.0% of the SC vs. 41.7% of the MAR), whereas the rate of mild birth weight discordance of (15 to 24.9%) was less frequent in this group (1/10, 10% of the SC vs. 18/60, 28.3% of the MAR). The percentage of neonates with severe discordance ( $\geq 25\%$ ) was very similar in both groups (3/10, 30.0% of the SC group vs. 30.0% of the MAR group). The total overview of the birth weight discordance distribution for both groups of triplets is given in (see annex 11).

Fetal gender distribution varies slightly between groups of twins where nearly half of neonates in both groups were males (52.4% in MAR vs. 50.6% in SC group), and the

remaining were females (47.6% of MAR vs. 49.4% of SC), this also applied for the triplet groups in which nearly half of the neonates in both groups were males (50.5% in MAR vs. 49.9% in SC) and the remaining were females (53.1% in SC vs. 49.5% in MAR). A small difference was found between the groups.

The rate of same sex twins was more frequent among the SC group than among the MAR group (66.2% of the SC vs. 51.2% of the MAR), where the rate of different-sex twins was less frequent in this group (33.8% of the SC vs. 48.8% of the MAR). Among twins with the same sex; in the SC group (50.5% were males and 49.5% were females), while in the MAR group, (54.1% were males and 45.9% were females). Among triplet groups, the neonates were mostly of different sex, but the rate was higher among the MAR group than among the SC group (80.0% of the MAR vs. 7/10, 70.0% in SC), whereas (20.0% of the MAR vs. 3/10, 30.0% of the SC) were of the same sex neonates. Of the three same sex sets in the SC. group, one set was all males and 2 sets were all females, as for the 12 same sex sets in the MAR group, six sets were all males and six sets were all females.

Although the percentage of twins who had Apgar score <7 at birth was relatively low in both groups, the percentage was higher in the MAR group (23.9% of the MAR vs. 11.4% of the SC group). At 5 minutes, 5.2% of twin neonates in the MAR group had Apgar score <7 compared to 4.4% of those in the SC group, hence very similar percentages were observed. In both groups of triplets, the incidence of Apgar score <7 at one minute of delivery was also higher in the MAR group (62.9% of the MAR group vs. 43.8% of the SC group). At 5 minutes, the incidence of Apgar score <7 was slightly higher in the MAR group (14.0% of the MAR vs. 12.5% of the SC).

Table 4.11-A: Characteristics of the multiple birth neonates for the SC and MAR groups

Parameters	Twins N=1381		Triplets N=216	
	SC	MAR	SC	MAR
	N =942	N =439	N=32	N=184
<b>Gestational age (weeks)</b>				
Mean (SD)	36.1 (2.9)	35.4 (2.7)	32.5 (2.8)	32.3 (2.6)
<32	68 (7.2%)	34 (7.7%)	14 (43.7%)	51 (27.7%)
32-36	412 (43.7%)	237 (54.0%)	18 (56.3%)	133 (72.3%)
≥37	462 (49.0%)	168 (38.3%)	—	—
<b>Birth weight (grams)</b>				
Mean (SD)	2402.6 (582.2)	2275.6 (614.7)	1704.5 (426.6)	1618.9 (466.2)
<1500	58 (6.2%)	45/433 (10.4%)	10 (31.3%)	62 (33.7%)
1500-2500	418 (44.4%)	225/433 (52.0%)	22 (68.7%)	115 (62.5%)
≥2500	466 (49.4%)	163/433 (37.6%)	—	7 (3.8%)
<b>Gender</b>				
Male	477 (50.6%)	230 (52.4%)	15 (46.9%)	93 (50.5%)
Female	465 (49.4%)	209 (47.6%)	17 (53.1%)	91 (49.5%)
<b>Sex concordance</b>				
Same sex set	307 /464 (66.2%)	111/217 (51.2%)	3/10 (30.0%)	12 /62(20.0%)
Different sex set	157/464 (33.8%)	106/217 (48.8%)	7 /10(70.0%)	48/62 (80.0%)

Table 4.11-B: Characteristics of the multiple birth neonates for the SC and MAR groups

APGAR score				
1 minute				
<7	106/929 (11.4%)	104/435 (23.9%)	14/32 (43.7%)	112/178 (62.9%)
≥7	823/929 (88.6%)	331/435 (76.1%)	18 /32(56.3%)	66 /178(37.1%)
5 minutes				
<7	40/905 (4.4%)	22/426 (5.2%)	4 /32(12.5%)	25/178 (14.0%)
≥7	865/905 (95.6%)	404/426 (94.8%)	28 /32(87.5%)	153/178 (86.0%)

*Note.*

SC, spontaneous conception; MAR, medical assisted reproduction; SD, standard deviation.

### 4.6.3. Neonatal morbidity and mortality for the whole multiple birth groups

Table (4.12) demonstrated that 73.0% of the twins and all triplets and quadruplets neonates had adverse neonatal outcomes. Consequently, only 27.0% of the twins were delivered normally (delivered with  $\geq 37$  weeks of gestation, with normal birth weight and Apgar score  $>7$  at one and 5 minutes, with no need to NICU admission). In the present study, about half of the twins 53.8%, (856/1591) and all of triplets and quadruplets were premature, and about half the of twins 54.0% (854/1582), all except seven neonates of triplets and all quadruplet neonates had birth weight  $<2,500$  g. In the present study, Admission to NICU was needed for 43.1% of twins, 94.7% of triplets and for all quadruplets. The median number of admission days in twins group was (5 days, minimum=0.5; maximum=210), while in triplets group it was (14.5 days, minimum=0.5; maximum=93), and in quadruplet group (27 days, minimum=5 days; maximum=57 days).

In the current study, the most common adverse neonatal outcomes were the respiratory problems, mainly the respiratory distress syndrome which occurred for 28.4% of the twins, 91.3% of the triplets and 88.9% of the quadruplets. Among them, resuscitation was required for the majority of twins (99.5%), triplets (98.8%), and for all quadruplets. Phototherapy was used for 13.3% of the twins, 55.4% of the triplets and 83.3% of the quadruplets. Sepsis occurred in 3.1% of the twins, 8.7% of the triplets and in (3/18, 16.7%) of the quadruplets (blood borne sepsis was prominent). Sixty one neonates (4.7%) of the twin group developed hematologic problems, as well as 28.8% of the triplets, and 66.7% of the quadruplets (neonatal anemia that required blood transfusion was more distinguishable).

In twin births, there were 64 (4.4%) malformed neonates. The anomalies included 19 who had musculoskeletal abnormality, 17 who had genitourinary anomaly, 11 who had central nervous system anomalies, 10 who had cardiovascular problems, one who had cystic hygroma, one who had congenital hypothyroidism, one who had ecchymosis, one who had imperforate anus and 12 who had other anomalies. In the triplets group, (9/200, 4.4%) neonates had anomalies. The anomalies included three who had cardiovascular problems, three who had genitourinary anomalies, two who had musculoskeletal abnormality, one who had a central nervous system anomaly, and the last case was found with

hemangioma. In the quadruplet group, (7/23, 30.4%) neonates had anomalies, among that, four had muscle skeletal anomalies, two had cardiovascular anomalies, and one had central nervous systems anomalies.

In addition to anomalies reported above, according to the information reported by mothers, 40 additional twin newborns had anomalies. The anomalies reported by mothers included 15 congenital heart diseases, seven inguinal hernia, two umbilical hernia, two undescended testicles, five congenital hip dysplasia, three hypospadias, three syndactyly, one polydactyly, and two central nervous system malformations, and one cleft palate. Furthermore, fifteen mothers having twins reported lower limb problems and two mothers reported upper limb problems. Four mothers of triplets also reported an anomaly in their newborns. Among those, one mother reported congenital heart disease, two inguinal hernias, and one developmental dysplasia of the hip.

In the current study, the less frequent neonatal complications included iatrogenic respiratory problems (iatrogenic disease is the result of diagnostic and therapeutic procedures undertaken on a patient) (Krishnan and Kasthuri, 2005). These complications include pneumothorax, pulmonary hemorrhage, Bronchopulmonary Dysplasia, and the interstitial emphysema that occurred in 0.9% of twins and in (9/184, 4.9%) of triplets. In addition to necrotizing enterocolitis which occurred in (8/1311, 0.6%) of twins and in (4/184, 2.2%) of triplets, Intra ventricular hemorrhage in (5/1311, 0.4%) of twins and in (7/184, 3.8%) of triplets, and patent ductus arteriosus which occurred in (3/1311, 0.2%) of twins and in (2/184, 1.1%) of triplets.

There were 57.2 per 1000 (87/1522, 5.7%) perinatal deaths in the twin group and 141.6 per 1000 (32/226, 14.2%) in triplets and 41 per 1000 (1/24, 4.2%) in quadruplets. Neonatal death occurred in 5.7% of twin groups, 15.1% of triplets and 8.7% of quadruplets. The majority in both twins (62/85, 73.0%), and triplets (25/33, 75.8%) died during the early neonatal period. Perinatal and neonatal mortality was not affected by mothers' age and parity. Early and late neonatal death was associated with the lower gestational age. Death >28 days was recorded for 0.8% in the twins group and in (8/219, 3.6%) in the triplets group.

Table 4.12: Neonatal morbidity and mortality of multiple births of all of the multiple birth groups

Complications	Multiple births N= 1853	
	Twins N=1591	Triplets and quadruplets N=262
Yes	1137/1559 (73.0%)	262 (100.0%)
Prematurity (<37 weeks)	856/1591 (53.8%)	262 (100.0%)
Birth weight (<2500 gm)	854/1582 (54.0%)	254/261 (97.3%)
NICU admission	659/1528 (43.1%)	236/248 (95.2%)
Mean duration (SD) (days)	9.6 (13.6)	17.9 (14.6)
Median (days)	5.0	15.0
(Minimum, Maximum) (days)	(0.5, 210)	(0.5, 93)
	<b>N=1311</b>	<b>N=202</b>
Respiratory disorders †	372 (28.4%)	184 (91.1%)
Respiratory support ‡	370 (99.5%)	182 (98.9%)
Iatrogenic respiratory problems §	12 (0.9%)	9 (4.5%)
Need phototherapy	174 (13.3%)	117 (57.9%)
Necrotizing enterocolitis	8 (0.6%)	4 (2.0%)
Intra ventricular hemorrhage	5 (0.4%)	7 (3.5%)
Sepsis ¶	40 (.1%)	19 (9.4%)
Patent ductus arteriosus	3 (0.2%)	2 (1.0%)
Hematologic problems #	61 (34.7%)	65 (32.2%)
Abnormality *	64/ 1407(4.4%)	16/ 223(7.0%)
Other complications **	66 (5.0%)	16 (7.9%)
<b>Perinatal Mortality</b>	<b>N=1522</b>	<b>N=250</b>
Perinatal mortality	87 (5.7%)	33 (13.2%)
	<b>N=1497</b>	<b>N=242</b>
Neonatal death	85 (5.7%)	35 (14.5%)
Early	62 (73.0%)	25 (71.4%)
Late	23 (27.0%)	10 (28.6%)

Note.

NICU: neonatal intensive care unit.

†Respiratory disorders include: respiratory disorder syndrome, transient tachypnea of the newborn, grunting, bronchiolitis, retractions, distressed newborns (please refer to annex 12).

‡Respiratory support include: O2 therapy, mechanical ventilator, CPAP, and surfactant (please refer to annex 13).

§Iatrogenic respiratory problems include: Pneumothorax, pulmonary hemorrhage, bronchopulmonary dysplasia, interstitial emphysema (please refer to annex 14).

¶Sepsis includes: blood sepsis, pneumonia, UTI, meningitis (please refer to annex 15).

#Hematologic problems include: need PRBC, DIC, anemia, coagulopathy, and thrombocytopenia (please refer to annex 16).

\* More details on the types of abnormalities will be given in the annex 18-23.

\*\*Other neonatal complications (please refer to annex 17).

#### **4.6.4. Neonatal morbidity and mortality of multiple births according to the method of conception (SC, MAR group)**

It is evident from the Table (4.13) that twins in the medically assisted conception group were more likely to develop complications than in the spontaneous group (80.8% of the MAR group vs. 68.3% of the SC group). Consequently, only 19.2% of the neonates in the MAR group were healthy, weighing >2,500 g, had an Apgar score of >7 at one and 5 minutes, no malformations, no complications and were not admitted to NICU. In comparison, such neonates were found in 31.7% of SC twin groups. Among triplet groups, all of the neonates from SC group and MAR group had adverse neonatal outcomes.

In this study, the percentage of premature neonates was higher in the MAR group (61.7% of the MAR vs. 51.0% of the SC group), as were birth weight <2,500 g (62.4% of the MAR vs. 50.5% of the SC group), NICU admission (51.5% of the MAR vs. 39.6% of the SC group), respiratory problems (35.7% of the MAR vs. 26.4% of the SC group), and use of phototherapy (20.7% of the MAR group vs. 11.0% of the SC group). The duration of stay in the NICU was also longer for the MAR group (median 7.0 days for the MAR vs. 4.0 days for the SC group). There was no difference between the two groups in terms of respiratory problems treatments as 99.5% in the SC group needed surfactant and assisted ventilation compared to 99.2% in the MAR group.

Hematologic problems were slightly higher in the MAR group (7.6% of the MAR vs. 3.4% of the SC group) as were sepsis (4.6% of the MAR vs. 2.5% of the SC), and the other neonatal complications (6.3% of the MAR vs. 4.7% of the SC). The percentage of neonates with congenital abnormalities was very similar in both groups (4.3% in the MAR vs. 4.2% of the SC) as were iatrogenic respiratory problems (5/367, 1.4% of the MAR vs. 7/825, 0.8% of the SC), necrotizing enterocolitis (3/367, 0.8% of the MAR vs. 5/825, 0.6% of the SC), Intra ventricular hemorrhage (3/825, 0.4% of the SC vs. 1/367, 0.3% of the MAR), and patent ductus arteriosus (1/367, 0.3% of the MAR vs. 2/825, 0.2% of the SC).

All of the triplet neonates in both groups were premature. All of the neonates in the SC group and all except seven neonates in the MAR group had birth weight <2,500 g. The incidence of respiratory problems was higher in the MAR group (92.3% in MAR vs. 83.3% in the SC). All of the neonates with respiratory problems in both groups needed respiratory support. The use of phototherapy was also higher in the MAR group (60.1% of the MAR vs. 40.0% of the SC group), as were hematologic problems (30.1% of the MAR triplets vs. 5/30, 16.7% of the SC group). The duration of stay in the NICU was also longer in the MAR group (median 15.0 days for the MAR vs. 9.0 days for the SC group). The percentage of NICU admission was slightly higher in the MAR group (94.9% of the MAR vs. 90.6% of the SC). Whereas the incidence of sepsis was slightly lower in the MAR group (8.4% of the MAR vs. 3/30, 10.0% of the SC), as were Intra ventricular hemorrhage (5/143, 3.5% of the MAR vs. 2/30, 6.7% of the SC), and the congenital anomalies (6/155, 3.3% of the MAR vs. 3/32, 9.4% of the SC). Of the three cases in SC group, one had ventricular septal defect, another one had proximal lap stenosis, and one with hypospadias, and among the six cases in the MAR, one had tetralogy of fallot,

ventricular septal defect, pulmonary valve stenosis and polycystic kidney, two with club foot, one had undescended testicles, ambiguous genitalia with severe chordate, one had hydrocephalus, and the last one had hemangiomas.

The incidence of other complications was also lower in the MAR group (7/143, 4.9% of the MAR vs. 5/30, 16.7% of the SC). The incidence of Necrotizing enterocolitis was very similar in both groups (1/30, 3.3% of the SC vs. 3/143, 2.1% of the MAR), as were iatrogenic respiratory problems (1/30, 3.3% of the SC vs. 4/143, 2.8% of the MAR group). The patent ductus arteriosus was recorded for two neonates (1.4%) in the medical assisted conception group.

Similarly, the perinatal and neonatal mortality rate did not differ among the groups of twins, there were 56.2 per 1000 (24/427, 5.6%) perinatal deaths in the MAR compared to 55.5 per 1000 (53/955, 5.5%) in the SC group, and there were 5.9% neonatal deaths in the MAR group compared to 5.4% in SC group, in which the majority of neonates in both groups (39/51, 76.5% of the SC vs. 19/25, 76.0% of the MAR) died during the early neonatal period. Among triplets; perinatal mortality was slightly higher in the SC group (5/33, 15.2% of the SC vs. 11.4% of the MAR group), as well as the neonatal mortality which occurred in (4/32, 12.5% of the SC vs. 10.5% of the MAR group), in which all of those in the SC group and the majority (15/18, 83.3%) in the MAR group died during early neonatal period.

Table 4.13-A: Neonatal morbidity and mortality of multiple births for the SC and MAR groups

Parameters	Twins N=1381		Triplets N=216	
	SC N=942	MAR N=439	SC N=32	MAR N=184
<b>Neonatal complications</b>				
Yes	643/942 (68.3%)	354/438 (80.8%)	32 (100.0%)	184(100.0%)
Prematurity (<37 weeks)	480/942 (51.0%)	271/439 (61.7%)	32 (100.0%)	184 (100.0%)
Birth weight (<2500 gram)	476/942 (50.5%)	270/433 (62.4%)	32 (100.0%)	177/184 (96.2%)
NICU admission	373/942 (39.6%)	221/429 (51.5%)	29/32 (90.6%)	166/175 (94.9%)
Mean duration (SD) (days)	8.6 (14.4)	11.5 (12.6)	13.7 (14.7)	17.6 (13.9)
Median (days)	4.0	7.0	9.0	15.0
(Minimum, Maximum) (days)	(0.5, 210)	(0.5, 62)	2.0-48.0	0.5-93.0
	<b>N=825</b>	<b>N=367</b>	<b>N=30</b>	<b>N=143</b>
Respiratory disorders	219 (26.4%)	131 (35.7%)	25 (83.3%)	132 (92.3%)
Respiratory support	217 (99.5%)	130 (99.2%)	25 (100.0%)	132 (100.0%)
Iatrogenic respiratory problems	7 (0.8%)	5 (1.4%)	1 (3.3%)	4(2.8%)
Need phototherapy	91 (11.0%)	76 (20.7%)	12 (40.0%)	86(60.1%)
Necrotizing enterocolitis	5 (0.6%)	3 (0.8%)	1 (3.3%)	3 (2.1%)
Intra ventricular hemorrhage	3 (0.4%)	1 (0.3%)	2 (6.7%)	5 (3.5%)

Table 4.13-B: Neonatal morbidity and mortality of multiple births for the SC and MAR groups

Sepsis	21 (2.5%)	17 (4.6%)	3 (10.0%)	12 (8.4%)
Patent ductus arteriosus	2 (0.2%)	1 (0.3%)	—	2 (1.4%)
Hematologic problems	28 (3.4%)	28 (7.6%)	5 (16.7%)	43 (30.1%)
Abnormality	40/ 894(4.2%)	19/394 (4.3%)	3/32 (9.4%)	6/155 (3.3%)
Other complications	39 (4.7%)	23 (6.3%)	5 (16.7%)	7 (4.9%)
<b>Perinatal Mortality</b>	<b>N=955</b>	<b>N=427</b>	<b>N=33</b>	<b>N=176</b>
Perinatal mortality	53 (5.5%)	24 (5.6%)	5 (15.2%)	20 (11.4%)
	<b>N=941</b>	<b>N=422</b>	<b>N=32</b>	<b>N=171</b>
Neonatal death	51 (5.4%)	25 (5.9%)	4 (12.5%)	18 (10.5%)
Early neonatal death	39 (76.5%)	19 (76.0%)	4 (100.0%)	15 (83.3%)
Late neonatal death	12 (23.5%)	6 (24.0%)	—	3 (16.7%)

*Note.*

SC, spontaneous conception; MAR, medical assisted reproduction.

More details on the frequency distribution of the types of respiratory disorders, respiratory support, iatrogenic respiratory problems, hematologic problems, abnormalities, and other complications dispersed according to the method of conception will be given in the annexes 12-23.

#### 4.7 Neonatal outcomes of multiple births neonates according to the type of MAR (IVF, IUI and IOO)

We further studied the neonatal outcomes of multiple births according to the different types of MAR, including IVF, IUI, and IOO (Tables, 4.14 and 4.15). Among twin groups, neonates in the IUI group were delivered on average one week earlier than those in the IVF and IOO group (34.5 weeks, SD 3.7 in the IUI vs. 35.4 weeks, SD 2.3 in the IVF vs. 35.6 weeks, SD 3.1 weeks in the IOO). Twin neonates that resulted after IUI conception were also slightly lighter than those in other groups (mean 2227.2, SD 742.1 g of the IUI vs. 2260.8, SD 514.5 g of the IVF vs. 2294.5, SD 700.7 g of the IOO), and had more sets with different sexualities in the IUI group (6/9, 66.7% of the IUI vs. 48.6% of the IVF vs. 47.5% of the IOO group).

The percentage of premature neonates was lower in the IOO group than in the other groups (53.2% of the IOO vs. 67.6% of the IVF vs. 77.8% of the IUI), as was the NICU admission (46.3% of the IOO vs. 55.6% of the IUI vs. 56.2% of the IVF), but the neonates in the IOO group had longer hospital stay (median 8.0 days of the IOO vs. 5.5 days of the IVF vs. 5.0 days of the IUI group) as compared with other groups. The IVF neonates were more likely than those in other groups to have birth weight less than 2,500 g (67.8% of the IVF vs. 57.2% of the IOO vs. 56.3% of the IUI), and had higher incidence of an apgar score of <7 at one minute of delivery (28.5% of the IVF vs. 19.9% of the IOO vs. 3/16, 18.7% of the IUI group).

Among triplet groups, triplet neonates in the IUI were also delivered on average one week earlier than IVF and IOO group (31.0 weeks, SD 3.1 in the IUI vs. 32.5 weeks, SD 2.3 in the IVF vs. 32.4 weeks, SD 3.2 weeks in the IOO). The mean birth weight was similar in

the IUI and IOO group, but it was lower in the IVF group with an average of 187g (1668.5g, SD 441.5 in the IVF vs. 1482.8g, SD 407.6 in the IUI vs. 1481.8g, SD 564.9 in the IOO group). However, neonates after IUI conception were more likely than those in other groups to have birth weight <1,500g (61.1% of the IUI vs. 41.9% of the IOO vs. 28.2% of the IVF group), and less likely to have birth weight between 1,500 to 2,500g (6/18, 33.3% of the IUI vs. 58.1% of the IOO vs. 67.6% of the IVF). They also had higher different sex neonates (6/6, 100% of the IUI vs. 80.0% of the IOO group vs. 77.3% of the IVF). In addition, triplet neonates resulting from IUI conception had higher occurrence of hematologic problems (7/16, 43.8% of the IUI vs. 9/26, 34.6% of the IOO group vs. 26.7% of the IVF group), and needed longer hospital stay (median 34.0 days for the IUI vs. 16.0 days for the IVF vs. 10.0 days for the IOO group) than those in the other groups.

There were more male neonates in the IOO group than in other groups (64.5% of the IOO group vs. 55.6% of the IUI vs. 46.7% of the IVF group). The incidence of apgar score <7 at 5 minutes of delivery was also higher in the IOO group (7/31, 22.6% of the IOO vs. 3/18, 16.7% of the IUI vs. 11.6% of the IVF group). Neonates resulting from IOO conception had higher perinatal mortality rate (8/33, 24.2% of the IOO vs. 12/126, 9.5% of the IVF vs. 0.0% of the IUI), and neonatal mortality rate (7/31, 22.6% of the IOO vs. 11/123, 8.9% of the IVF vs. 0.0% of the IUI). Furthermore, this study indicated that the use of phototherapy was higher in the IVF group compared to other groups (66.3% of the IVF vs. 8/16, 50.0% of the IUI vs. 42.3% of the IOO group).

After Stratification of neonatal complications by the gestational age and birth weight, the risk of complications was the highest for newborns with low gestational age and low birth weight. Stratification of neonatal complications by mothers' age and parity revealed that these complications were independent from mother's age and parity, except for the prematurity, as reported previously, that was found higher for the mothers aged less than 30 years old. Furthermore, the neonatal complications were independent from the newborn's gender.

Table 4.14: Characteristics of the multiple birth neonates according to the type of MAR (IVF, IUI and IOO)

Parameters	Twins N= 435			Triplets N=184		
	IVF	IUI	IOO	IVF	IUI	IOO
	N=216	N=18	N=201	N=135	N=18	N=31
<b>Gestational age (weeks)</b>						
Mean (SD)	35.4 (2.3)	34.5 (3.7)	35.6 (3.1)	32.5 (2.3)	31.0 (3.1)	32.4 (3.2)
<32	12 (5.6%)	4 (22.2%)	18 (9.0%)	36 (26.7%)	6 (33.3%)	9 (29.0%)
32-36	134 (62.0%)	10 (55.6%)	89 (44.2%)	99 (73.3%)	12 (66.7%)	22 (71.0%)
≥37	70 (32.4%)	4 (22.2%)	94 (46.8%)	—	—	—
<b>Birth weight (gram)</b>						
Mean (SD)	2260.8 (514.5)	2227.2 (742.1)	2294.5 (700.7)	1668.5 (441.5)	1482.8 (407.6)	1481.8 (564.9)
<1500	12/214 (5.6%)	3/16 (18.8%)	30 (14.9%)	38 (28.2%)	11 (61.1%)	13 (41.9%)
1500-2500	133/214 (62.2%)	6/16 (37.5%)	85 (42.3%)	91 (67.4%)	6 (33.3%)	18 (58.1%)
≥2500	69/214 (32.2%)	7/16 (43.7%)	86 (42.8%)	6 (4.4%)	1 (5.6%)	—
<b>Gender</b>						
Male	115 (53.2%)	8 (44.4%)	106 (52.7%)	63 (46.7%)	10 (55.6%)	20 (64.5%)
Female	101 (46.8%)	10 (55.6%)	95 (47.3%)	72 (53.3%)	8 (44.4%)	11 (35.5%)
<b>Sex concordance-</b>						
Same sex set	55/107 (51.4%)	3/9 (33.3%)	52/99 (52.5%)	10/44 (22.7%)	—	2/10 (20.0%)
Different sex set	52/107 (48.6%)	6/9 (66.7%)	47/99 (47.5%)	34/44 (77.3%)	6 /6(100.0%)	8/10 (80.0%)
<b>Apgar score</b>						
1 minute						
<7	61/214 (28.5%)	3/16 (18.7%)	40 (19.9%)	83/129 (64.3%)	12 (66.7%)	17 (54.8%)
≥7	153/214 (71.5%)	13/16 (81.3%)	161 (80.1%)	46/129 (35.7%)	6 (33.3%)	14 (45.2%)
5 minutes						
<7	8/210 (3.8%)	1/16 (6.2%)	13/196 (6.6%)	15/129 (11.6%)	3 (16.7%)	7 (22.6%)
≥7	202/210 (96.2%)	15/16 (93.8%)	183/169 (93.4%)	114/129 (88.4%)	15 (83.3%)	24 (77.4%)

Note.

IVF, in vitro fertilization; IUI, Intrauterine insemination; IOO, Induction of ovulation; SD, standard deviation.

Table 4.15: Neonatal morbidity and mortality of multiple births according to the type of MAR (IVF, IUI and IOO)

Parameters	Twins N=435			Triplets N=184		
	IVF N=216	IUI N=18	IOO N=201	IVF N=135	IUI N=18	IOO N=31
<b>Neonatal complications</b>						
Yes	192/215 (89.3%)	16/18 (88.9%)	142/201 (70.6%)	135 (100.0%)	18 (100.0%)	31 (100.0%)
Prematurity (<37 weeks)	146/216 (67.6%)	14/18 (77.8%)	107/201 (53.2%)	135 (100.0%)	18 (100.0%)	31 (100.0%)
Birth weight (<2500 grams)	145/214 (67.8%)	9/16 (56.3%)	115/201 (57.2%)	129/135 (95.6%)	17/18 (94.4%)	31 (100.0%)
NICU admission	118/210 (56.2%)	10/18(55.6 %)	93/201 (46.3%)	119/126 (94.4%)	18/18 (100.0%)	29/31 (93.5%)
Mean duration (SD) (days)	9.5 (10.7)	12.9 (14.4)	13.8 (14.2)	17.7 (13.8)	28.1 (14.7)	10.6 (9.8)
Median (days)	5.5	5.0	8.0	16.0	34.0	10.0
Minimum-maximum	(0.5, 62)	(1, 35)	(0.5,60)	(0.5, 93.0)	(6.0, 54.0)	(0.5, 44.0)
	<b>N=174</b>	<b>N=15</b>	<b>N=178</b>	<b>N=101</b>	<b>N=16</b>	<b>N=26</b>
Respiratory disorders	68 (39.1%)	5 (33.3%)	58 (32.6%)	93 (92.1%)	16 (100.0%)	23 (88.5%)
Respiratory support	67 (98.5%)	5 (100.0%)	58 (100.0%)	94/93 (100.0%)	16 (100.0%)	23 (100.0%)
Iatrogenic respiratory problems	3 (1.7%)	—	2 (1.1%)	3 (3.0%)	—	1 (3.8%)
Need phototherapy	43 (20.0%)	3 (16.7%)	30 (14.9%)	67 (66.3%)	8 (50.0%)	11 (42.3%)
Necrotizing enterocolitis	—	1 (6.7%)	2 (1.1%)	3 (3.0%)	—	—
Intra ventricular hemorrhage	—	—	1 (0.6%)	4 (4.0%)	—	1 (3.8%)
Sepsis	6 (3.4%)	—	11 (6.2%)	9 (8.9%)	—	3 (11.5%)
Patent ductus arteriosus	—	—	1 (0.6%)	1 (0.7%)	—	1 (3.2%)
Hematologic problems	11 (6.3%)	1 (6.7%)	16 (9.0%)	27 (26.7%)	7 (43.8%)	9 (34.6%)
Abnormality	9/ 194 (4.2%)	1/15 (5.6%)	9/185 (4.5%)	5/108 (3.8%)	1/17 (5.6%)	—
Other complications	11 (6.3%)	3 (20.0%)	9 (5.1%)	5 (5.0%)	1 (6.3%)	1 (3.8%)
Perinatal Mortality	<b>N=208</b>	<b>N=15</b>	<b>N=204</b>	<b>N=126</b>	<b>N=17</b>	<b>N=33</b>
	6 (2.9%)	—	18 (8.8%)	12 (9.5%)	—	8 (24.2%)
Neonatal death	<b>N=206</b>	<b>N=15</b>	<b>N=201</b>	<b>N=123</b>	<b>N=17</b>	<b>N=31</b>
	7 (3.4%)	—	18 (9.0%)	11 (8.9%)	—	7 (22.6%)
Early	4 (57.1%)	—	15 (83.3%)	9 (81.8%)	—	6 (85.7%)
Late	3 (42.9%)	—	3 (16.7%)	2 (18.1%)	—	1 (14.3%)

Note.

IVF, In vitro fertilization; IUI, Intrauterine insemination; IOO, Induction of ovulation.

More details on the types of respiratory disorders, respiratory support, iatrogenic problems, hematologic problems, other complications and abnormalities dispersed according to the method of conception will be given in the annex 12-23.

## Summary

During the study period, multiple births occurred in 2.2% of cases, of which 89.9% were twins and 10.1% were triplets and quadruplets. According to methods of multiple births conception, the rate of twins spontaneously conceived was higher (68.3%), while the rate of triplets (85.3%) and quadruplets (4/6, 66.7%) conceived by MAR was higher. Among the types of MAR evaluated; IVF and IOO were the most favorable techniques for the women with multiple births, and the IUI was rarely used.

The women of twins and triplets in the medical assisted conception group were younger, had higher university education, had lower parity, and they were more frequently performing the cervical stitch. Furthermore, the majority of couples in the medical assisted conception group had a history of infertility, and were more often reported living in north WB. Family history of multiple births, history of abortion and giving births in public hospitals were higher in the SC group of twins and triplets. In the SC group of twins there were more housewives, and more of consanguineous marriage and births seen in south WB. Small differences between SC and MAR group of twins and triplets were for parental consanguinity, where around quarter of them resulted after consanguineous marriage. A small difference was found in the personal history category of multiple births among groups of triplets where few cases had a personal history. A small difference was found as well in the work status of women category among groups of twins where the majority were housewives. In terms of personal history of multiple births among twins in both SC group and MAR group, the results were similar.

Women with twins in the MAR group had higher preterm delivery, and cesarean delivery in which the emergency cesarean delivery was more frequent in the SC group than elective delivery. The prevalence of complications such as PPRM, hypertensive, antepartum hemorrhage, placental complications, and intrauterine growth restriction was slightly higher in the MAR group, whereas the incidence of anemia was lower in this group. Similar percentages between groups were found in the prevalence of fetal malpresentation, stillbirths, gestational diabetes mellitus, and other pregnancy complications, twin to twin transfusion syndrome, and postpartum hemorrhage. In triplet births, all women in SC and MAR group had preterm delivery and all except two women delivered by cesarean section in which the majority had an emergency procedure. The women in the SC group had higher anemia and hypertensive diseases. The prevalence of placental complications, stillbirth, other complications and postpartum hemorrhage was slightly higher in the SC group, whereas the occurrence of PPRM was slightly lower in this group. The occurrence of antepartum hemorrhage, and intrauterine growth restriction was only recorded in the MAR group.

The IOO-treated women with twins had higher parity, more frequently seen in south WB, and had less use of cervical stitch, they were less likely to have complications by preterm delivery and to have delivery by cesarean section. The IOO-treated women with triplets were younger, and had higher consanguineous marriage, and appeared to be less likely to develop anemia. The IOO-treated women with twins and triplets gave birth more often in

public hospitals, and reflected less infertility. Women with twins who underwent IUI treatment had higher university education, were employed, and were more often seen in middle WB, and they were more likely to have hypertensive complications, and less likely to have fetal mal-presentation. The IUI triplets were more often seen in north WB, more likely to have no previous births, and they were more likely to have PPRM. The IVF-treatment was associated with higher placement of cervical stitch among women with triplets.

This study has given an account of the neonatal outcomes, among the medically assisted conceived twin neonates. There were more neonates born <37 weeks gestation, more neonates with low birth weight, more Apgar score <7 at one minute of delivery, more NICU admission, use of phototherapy, more with respiratory problems and longer hospital stay in the MAR group of twins. Same sex twins were higher in the SC group. Small difference between SC and MAR group was for distribution of birth weight discordance where the majority had mild discordance, fetal gender where half were males and the other half were females, and incidence of sepsis, hematologic problems, and other neonatal complications where they were less frequent in both groups. Results were similar between groups in terms of incidence of Apgar score <7 at 5 minutes of delivery, incidence of severe birth weight discordance, use of respiratory problems treatments, the occurrence of congenital abnormalities, iatrogenic problems, necrotizing enterocolitis, intra ventricular hemorrhage, and patent ductus arteriosus, and perinatal and neonatal mortality rate.

The neonates of triplets in both groups had similar mean gestational age, and similar mean birth weight, all were premature and almost all of them had birth weight <2,500g. In the MAR group there were more neonates born between 32-36 weeks, and less neonates born <32 weeks gestation, more different sex sets, higher apgar score <7 at one minute of delivery, and more neonates with mild birth weight discordance, higher risk of respiratory disorders, hematologic problems, more that required phototherapy, and longer hospital stay. All of the neonates in both groups who developed respiratory problems needed respiratory support. The incidence of other complications was lower in the MAR group. Small differences between SC and MAR group were for NICU admission, where the majority needed care in the NICU, incidence of sepsis, IVH, congenital anomalies, perinatal and neonatal mortality rate where they were less frequent, and distribution of birth weight where most of them weighed between 1,500 to 2,500 g, fetal gender where nearly half of them were males and the other half were females and in the Apgar score <7 at 5 minutes of delivery where few cases had apgar score <7. Similar results were found in the incidence of NEC, and iatrogenic respiratory problems. PDA was found in the medical assisted conception group.

Among the three types of MAR evaluated, the IUI twin neonates were born earlier. Twin neonates born premature and needed NICU admission were less common in the IOO group, but needed longer hospital stay. The IVF twin neonates were more likely to weigh <2,500 g and had higher apgar score <7 at one minute of delivery. Among triplet groups, the IUI neonates were also born earlier, and had higher different sex sets, higher hematologic problems, and they needed longer hospital stay, and there were more neonates who weighed <1,500 g. In the IOO group, neonates had higher males, and higher incidence of apgar score <7 at 5 minutes, and had higher perinatal and neonatal mortality rate. The IVF triplets had higher use of phototherapy.

## **Chapter five**

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### **Discussion**

#### **Introduction**

The purpose of the discussion section in a research is to explain the meaning of the results to the readers (Hess, 2004). The purpose of this retrospective study was to identify the prevalence and method of conception of multiple births whether spontaneous or medical assisted conception, and their consequences on maternal and neonatal health. This chapter includes a discussion of major findings as related to literature prevalence of multiple births, type of conception, population characteristics, and maternal, obstetrical and neonatal outcomes. Also, included is a discussion on limitations of the study, and areas for future research, in addition to a brief summary. The results will be compared with other global and regional studies.

#### **5.1 Prevalence of multiple births**

The prevalence of multiple births in this study was 2.2%, which was in the line with the proportion reported by family health survey (2010) from the Palestinian Central Bureau of Statistics (PCBS) (2013) which showed that 2.9% of the women in this survey reported previous history of multiple births. This study also reflected a lower prevalence than that in the United States, according to the birth data from the National Center for Health Statistics (NCHS), the prevalence of multiple births in 2011 was 3.5% of all births (Kulkarni et al., 2013).

Among the five hospitals selected for this study, a high prevalence of multiple births was seen in Specialized Arab Hospital which may be explained by the fact that the hospital was giving referral services for cases of multiple pregnancies that were treated in the ART clinic named Razan Clinics which is connected to the obstetric unit of this hospital where deliveries were conducted.

In the recent study, as expected, twins are the most common type of multiple births; it accounts for 2.0% of all births and 89.9% of all multiple births. Twin prevalence in our study has been found to be lower than the prevalence found in the United States, in which 3.3% of all births were twin births by 2011 (Sunderam et al., 2014). The higher-order

multiple births in this study constituted 0.2% of all births and 10.1% of all multiple births were triplets and quadruplets. Our finding was at a higher rate than that in the United States in which 0.1% of all births were higher-order multiples by 2011 (Sunderam et al., 2014). Our results regarding the birth rate of triplets ((2.1 per 1000 births) is similar to Lamb et al. 's (2011) findings where the birth rate of triplets was (2.0 per 1000 births).

The observed increase in the prevalence of higher-order multiple births could be interpreted as being a result of practices of embryo transfer in ART treatment. Unfortunately, absence of data about this issue limited the analysis. The absence of monitoring for non-ART treatments and multiple births may also play a role for the increased prevalence of higher-order multiple births in our study. Using the fertility treatments increased the risk for conception with more than one baby up to 30% after gonadotropin and by 12% after clomiphene citrate (ASRM, 2012). With the increasing risk of multiple pregnancies after using the fertility drugs; these drugs should only be prescribed when appropriate resources are available to monitor patients adequately and multiple births resulting from the use of ART can be controlled by limiting the number of embryos transferred.

Another possible explanation for this is the limitation to the use of the multiple pregnancy reduction because of the ethical issues and considerations associated with fetal reduction. This is evident in our study as we found 6 (0.7%) cases of multiple births reduced. This result was too small compared with the result of Daniel et al. (2000) study who reported 22.3% of the ART and 6.9% of the IOO pregnancies that were reduced. Chi-Hong Ho et al. (2005) also reported that the fetal reduction procedure was performed for 17.6% of the ART, and for 16.1% of the IOO pregnancies. The ethical considerations of multi fetal pregnancy reduction should be weighed against that related to raising the children from high-order pregnancies. Prevention of high-order multifetal pregnancies is essential and requires careful monitoring of infertility therapies.

## **5.2 Prevalence of multiple births according to the method of conception (SC, MAR) and to the type of MAR (IVF, IUI and IOO)**

Among the spontaneously conceived multiple births; twins are the most frequent, then comes triplets and quadruplets as the least frequent (Grosignani, 2000). As a result, literature about the spontaneous conception of multiple births was available for twin births, while it was limited for the higher-order multiple births.

In this study, the majority of twins (68.3%) resulted from spontaneous conception; with a rate of (19.9 per 1000 births). This is in good agreement with that in Germany (65.6%) (Bamberg et al., 2012), and with intermediate rates seen in North Africa, America, Asia, Oceania, and Europe of 9-20 per 1000 births (Hoekstra et al., 2008). The prevalence in our study was lower than the prevalence reported in the United Kingdom (2007- 2009) by which 76% of twin births were as a result of spontaneous conception (Anabzahgan et al., 2014), whereas it was higher than the prevalence in Arab countries such as Egypt (17.7 per 1000 deliveries), and Jordan (14.4 per 1000 deliveries) (Smits & Monden, 2011). This

higher figure may be explained by the fact that the hospitals were giving referral service receiving cases of twin pregnancy from the surrounding health center and hospitals. In the present study, the prevalence of triplets after spontaneous conception (14.9%) was lower than that in Mieth et al. (2011) study which showed that (27.4%) of triplet births resulted after spontaneous conception.

The risk of multiple pregnancies after using MAR is high in comparison to spontaneous conception; this is because of the embryo transfer and ovulation induction (Adamson & Baker, 2004). In the present study, infertility and lower parity influenced the decision to use the MAR to get pregnant. The most favorable choice was the IVF and IOO technique. In this study, 31.7% of twin births were found as a result of the MAR (15.6% of all twin births resulted from conception assisted by IVF treatment, and 15.9% of all twin births resulted from conception assisted by IOO and IUI treatment). These findings were lower than that in Germany in which 34.4% of all twin births resulted from conception assisted by fertility treatments (Bamberg et al., 2014), and in the United States 36.0% in 2011 (Kulkarni et al., 2013). Furthermore, the prevalence of twins after IVF and non-IVF treatments in our study was lower than that in the United States in 2011, where 17% of twin births were as a result of IVF and 19% where as a result from non-IVF treatment (Kulkarni et al., 2013).

In our study the majority of higher-order multiple births (83.7%) resulted from MAR (58.7% of all higher-order multiple births resulted from conception assisted by IVF treatment, and 25.0% resulted from conception assisted by IOO and IUI treatment). We found much higher prevalence than the prevalence in the United States where by 2011 77% of higher-order multiple births resulted from MAR, and 32.2% were after IVF (kulkarni et al., 2013). But the prevalence in our study was lower than that in the United States where 45% of the higher-order multiple births were attributable to non-IVF fertility treatments (Kulkarni et al., 2013). It was also lower than that in Mieth et al. (2011) study where they found that 24.2% of triplet births and one set of quadruplets occurred after IOO conception.

The observed increase in the prevalence could be interpreted as being a result of practices related to embryo transferring in ART treatment and limiting the use of multifetal pregnancy reduction. Infertility treatment should be managed by a specialist who will choose the most appropriate treatment when using ovulation induction technique. Increased awareness of multiple births results from non-IVF fertility treatment may lead to improved medical practices patterns and could reduce the rate of multiple births. Furthermore, the increased higher-order multiple pregnancies in our country compared with other countries suggests that guidelines for limiting the number of embryos transferred in assisted reproductive technologies must be adopted.

### **5.3 Maternal and obstetrical results according to the method of conception (SC, MAR) and to the type of MAR (IVF, IUI and IOO)**

Regarding the maternal socio-demographic, medical and obstetric data, In the recent study, young mothers were more frequent among our population (almost all of the mothers were under the age of 40). A comparison of mothers' age in twin births spontaneously conceived with those conceived via MAR revealed that the medically assisted conceived pregnancies consisted of slightly younger mothers than those conceived spontaneously (the mean age of the mothers 28.2, SD 5.9 years for the SC group and 27.8, SD 4.5 years for the MAR group). In our study we demonstrated inconsistent results with the constantly increasing number of twin births as a consequence of MAR in older women (Anbazhagan et al., 2014; Bamberg et al, 2012; Chi-Hong Ho et al., 2005; Daniel et al., 2000; & Narine et al., 2003). Among the mothers of triplets, the mothers in the spontaneous group were older than those in the MAR group (the mean maternal age of triplet groups 30.3, SD 4.9 years for SC group and 27.3, SD 4.9 years for MAR group). Our findings are not compatible with Fennesy et al., 2015) where there were no significant differences in the mean mother's age for both groups ((32.9 SD 3.7 years for the ART vs. 31.6 SD 4.6 years for the spontaneous group).

A possible explanation for the younger maternal age in the MAR group may be that the early marriage is a very common tradition among the Palestinian families. Furthermore, when the couples get married at a young age fail to conceive, they seek treatment early. According to the Palestinian Central Bureau of Statistics (2012) the median age of females at first marriage was 18.0 years in 1997, whereas the median age at the first marriage was 20.1 years in West Bank for females in 2010. In addition, women in our country face pressure from their society and families to get married and after that to bear children early right after marriage. On the other hand, most of the mothers of twins and higher-order multiples are highly educated. For instance, 37.1% of twins and 40.3% of the mothers of higher order multiples had completed university education, so they started seeking help earlier.

Comparing the mothers' parity and infertility history in both groups of twins (SC and MAR) revealed that most of the mothers in the MAR group had a history of infertility 67.5% and less than half of them 45.5% were nulliparous. Although our findings support previous findings in (Anbazhagan et al., 2014; Daniel et al., 2000; & Domingues et al., 2014) studies who demonstrated lower parity and higher of infertility among the mothers of twins who conceived using the MAR, but the percentages were lower than that reported in these studies. Domingues et al. reported that 88.3% of the mothers of twins in the MAR group were nulliparous, and 92% of the women in the MAR twin group had infertility, Anabazagan et al. reported that 29% of the mothers in the MAR group had  $\geq 1$  birth, in contrast to our findings, where 54.0% of the mothers in the MAR group had  $\geq 1$  birth.

The explicit reason behind this difference in percentages of mothers who had lower parity in the MAR group among our study population and other populations from other studies is the traditions and the culture of the Palestinian society which encourages reproduction and

childbearing. It is well known that the Palestinians value large families; they prefer to have more children to keep on social security (Hammoudeh et al., 2013). Despite the advanced medical technology and knowledge in reproduction, traditions continue to exert influence on how the couples manage their reproduction. These traditions extend also to the infertile couples. So, it is not surprising to see the infertile couples seeking more treatment cycles, since the medically assisted techniques are becoming an increasingly more accessible and necessary option for them. Since these treatment techniques are used more often and they increase the risk of multiple pregnancies, it should take into consideration that the main goal of using the medically assisted techniques is to have a healthy newborn, while multiple pregnancies are considered as one of the adverse outcomes of using these techniques. Hence, more studies are needed to evaluate the pregnancy outcomes with each cycle of treatment.

The obstetric history for the mothers of the higher-order multiple births, after spontaneous and medically assisted conception, was not described in the available literature. We found that the mothers in the MAR group were less likely to have had previous births, and most of them had a history of infertility. For instance, 59.7% of the mothers of triplets and quadruplets in the MAR group were nulliparous in comparison to 23.1% of the mothers in the SC group. Infertility history was found in 83.0% of cases of the medically assisted conceived triplets and quadruplets.

Medically assisted conception is becoming a more common option for couples who experienced fertility problems (Anbazahgan et al., 2014). Advances in reproductive technology have led to several treatment options. One of these options is preconception sex selection. The current development in the field of preconception sex selection allows the married couples also to fulfill their wish to have a boy through available medical means. In this study, in spite of the small number of cases who use the sex selection technique, we were surprised to find that almost all of the mothers select the IOO for this purpose. To the best of our knowledge, the recent scientific advances that made highly reliable preconception sex selection are the pre implantation diagnosis or sperm separation by flow cytometry combined with IVF, and the use of ovulation induction medications and artificial insemination do not appear to be effective (Reubino & Schener, 1996). Couples should be advised and directed toward using the proper technique when they are seeking the MAR for the purpose of sex selection. However, the pregnancy outcomes should be also considered and trials should be always directed towards prevention of multiple births.

In our study, it is interesting to note that the mothers in the MAR more frequently performed the cervical stitch. Unfortunately, it is not clear from the medical records, however, whether the mothers had cervical incompetence or whether suture placement was elective. Information from other studies regarding this variable was only found in Fitzsimons et al study, who found that the incidence of cerclage was higher in the medically assisted conceived triplets group. In this study, twin births in both groups (SC and MAR) were more frequent in women with no previous medical diseases. Our finding is consistent with the finding in the (Domigues et al. 2014) study. Furthermore, twin births after spontaneous conception were more frequent in women who had a family history of

multiple births. This finding is also consistent with the finding from Domigues et al. study. Previous medical history and family history of multiple births were not addressed in the studies of triplet births, we found that triplet births in both groups were more frequent in women with no medical diseases, and triplet births after spontaneous conception were more frequent in women who had family history of multiple births.

The percentage of mothers who had previous history of abortion in this study was higher in the spontaneous group; this result may confirm that the abortion may not be considered as a cause of fertility issues or complications in subsequent pregnancies. Our findings did not agree with Chi- Hong Ho et al's (2005) results, where there was a lower percentage of previous miscarriage in the spontaneous group, which might be due to the smaller sample size of this study.

As for place of residence, the prevalence of twins and triplets after MAR is higher in north WB than in middle and south of WB. This could be due to the differences in clinical practices in the fertility clinics. There was an increase in the prevalence of twins after spontaneous conception in south WB, possibly due to conceiving at a higher age and multiparity in this country with respect to cultural practices and traditions.

The majority of deliveries happened in the public hospitals, knowing that public hospitals are the major recipients of deliveries, and the costs are minimal compared to private hospitals, also the majority of citizens have public insurance. The increased number of multiple MAR giving birth at private hospitals could be because of the increased anxiety and concern for the newborns' health.

The socio-demographic variables of mother's education, occupation, and consanguinity are not described in other studies for both twins and higher-order multiple births. Interestingly, we found that the mothers of twins and triplets in the MAR group had higher levels of education; most of them are employed, whereas there were more twins and triplets in the SC group resulting from consanguineous marriage.

Regarding the maternal and obstetrical outcomes, the increased risk to maternal and obstetrical complications from multiple births (twins and higher-order multiple births) such as preterm delivery, anemia, PPRM, hypertensive disorders, fetal mal-presentation, and cesarean delivery in our study were consistent with previous findings (Sebire, Jolly, Harris, Nicoladies, & Regan, 2001; Qazi, 2011).

Several studies evaluated the effect of mode of conception on pregnancy outcomes, these studies revealed inconsistent findings. Some studies found better pregnancy outcomes in the medically assisted conception group, whereas others reported similar pregnancy outcomes, while others found a higher risk of complications after the medically assisted conception (Domigues et al., 2014). Not surprising that the available literature regarding this issue remains inconclusive. Van Hooff and Lambalk (2001) mentioned that a number of factors may have contributed to these contradictory findings. One of these factors is the variation in methodology used in these studies.

In the present study, we found that the mothers of twins in the MAR group are more likely than those in the SC group to have preterm delivery, and cesarean delivery. Moreover, this study showed a slightly higher prevalence of PPRM, hypertensive problems, antepartum hemorrhage, and placental problems in the MAR group, whereas the prevalence of anemia was slightly lower in this group. Very similar prevalence was for the prevalence of IUGR, gestational diabetes mellitus, stillbirth, twin to twin transfusion syndrome, and other pregnancy complications.

The present results are in accordance with those reported by (Narine et al., 2003) who performed a retrospective study to compare the perinatal outcomes of twins conceived by MAR (IVF, IUI, and IOO) and demonstrated lower gestational age in the MAR group compared with spontaneous conception group. Adler-Leavy et al. (2007) also reported a lower gestational age in twins resulted from IVF conception compared with spontaneously conceived twins. A lower gestational age in the IVF group with higher incidence of preterm delivery was further found in Nasser et al. (2003) study that also compared maternal complications in spontaneous versus in vitro fertilization twins. Moreover, these results were consistent with the results from Anabazhagan et al. (2014) study, who found no significant increase of gestational hypertension/preeclampsia in the medically assisted conception group, as were gestational diabetes, placental abruption, and the antepartum hemorrhage, and Dominguez et al. (2014) study, who found no significant difference in the incidence of TTTS.

Our results were inconsistent with the results of Bamberg et al. (2012) study who showed a significant increase in pregnancy complications among the women who used the MAR in terms of peripartum hemorrhage, cervical insufficiency, PROM, amniotic membrane prolapsed, postpartum anemia, and hypothyroidism, and Domingues et al. (2014) study who found that the mothers in the medically assisted conception group had a higher risk for first trimester bleeding, gestational diabetes, and intrauterine growth discordance. The previously mentioned data together with our present results of shorter mean gestational age; higher preterm delivery support the argument that the twin pregnancies resulting from the medically assisted conception may have poorer outcomes than the spontaneously conceived group.

Fetal mal-presentation in multiple pregnancies has rarely been reported in previous studies. Apparently, fetal mal-presentation affects the method of delivery and the outcome of the pregnancy. According to our data, mal-presentation was found in 68.1% of twin pregnancies. Among cesarean delivery, 45% of them performed to manage this complication.

Several reasons were suggested that may account for the higher preterm delivery among the medically assisted conceived twins. In our study, the higher rate of preterm delivery in the MAR group may be associated with placement of cervical stitch which is more frequently used in this group. Cerclage placement was associated with a higher rate of preterm delivery when compared to mothers with twins managed without cervical cerclage. Anbazhagan et al. (2014) reported that the difference in the incidence of preterm delivery

among studies may be attributable to the increases of elective late preterm births in uncomplicated twin pregnancies in such studies. Indeed, we found that most of the late preterm twin deliveries in the MAR group had spontaneous onset of labor and only around one third of them had planned cesarean delivery due to obstetrical and maternal and fetal indications.

Anbazhagan et al. (2014) also reported that the higher rate of preterm delivery in the MAR group was due to maternal stress, subclinical pelvic infection, micronutrient deficiencies and environmental exposure that are prevalent in the sub-fertile population may account for higher preterm delivery in the MAR group in our study, the absence of information about the health background of the infertile couples limited this analysis.

Another factor that may influence pregnancy outcomes is the placental chorionicity (Daniel et al., 2000). It is concluded that the monochorionicity did not affect the maternal health during pregnancy. However, it increased the fetal risks and increased the incidence of preterm delivery (Carters, Bishop, Goetizinger, Tuuli, & Cahill, 2015). Unfortunately, in our study we had insufficient data regarding this issue which limited the analysis. However, it is expected to have better outcomes in the medically assisted twin pregnancies, due to a higher rate of dichorionic placentas found in this type of pregnancy. The embryo transfer and multiple ovulations account for the high rate of dichorionic placentas. Some researchers compared the outcomes of dichorionic spontaneously conceived twins with those conceived by MAR and found a higher incidence of preterm delivery and modest worse obstetric outcomes for primiparous mothers of the induced dichorionic twins (VanHoof & Lambalk, 2001).

Some studies found that the characteristics of mothers who were treated with MAR are known to be older and primiparous plays a role in occurrence of pregnancy complications (Daniel et al., 2000). Those women are known to be at a higher risk for pregnancy complications. In our study the majority women in MAR group are with younger age, and the pregnancy complications were independent of mothers' age and parity, with the exception for the preterm delivery which was found among the mothers with age <30 years and also it was found higher among the mothers with lower parity in particular the mothers who were nulliparous.

Other investigators assumed that the ART procedure by itself or other patient characteristics may adversely affect the outcome (Daniel et al., 2000). Unfortunately, data about those patients were not available in the medical records. Supporting another factor that may affect the outcomes is the fetal reduction. Whether fetal reduction affects pregnancy outcome or not is controversial (Daniel et al., 2000). In our study, analysis of the effect of fetal reduction on pregnancy outcomes was hampered by the very small number of cases.

Information specifically addressing the maternal and obstetrical outcomes in triplet births arising from spontaneous conception compared with those resulting from the MAR is limited. The few existing studies lacked any significant difference, due to the small number

of populations used in these studies. Our study adds information to the limited available literature despite a small number of population in particular after spontaneous conception.

Among triplet groups, the prevalence of anemia and hypertensive was higher in the SC group, the prevalence of stillbirth, placental complications, and other pregnancy complications was slightly higher in the SC group whereas the prevalence of PPRM was slightly lower in this group. Cases with antepartum hemorrhage and intrauterine growth restriction were found only in the MAR group. The observed increase in the prevalence of anemia could be interpreted as being a result of inadequate treatment in antenatal care, and possible reason for the increased prevalence of hypertensive disorders is higher maternal age in this group.

Our results share a number of similarities with Fitzsimons et al.'s (1998) findings, where there were no significant differences between triplets after ART treatment and SC conception in terms of (rate of preterm labor, PROM, and gestational diabetes mellitus) and with Fennessy et al.'s (2015) findings where they found no significant difference in the ART group and SC group in the incidence of preterm delivery, PPRM, gestational diabetes mellitus, preeclampsia, placental abruption, TTTS, and fetal death. Fitzsimons et al. and Fennessy et al. found no significant difference between groups in the incidence of hypertensive disorders, our results do not corroborate with their results.

As regards to mode of delivery, our results were consistent with the anticipated trends observed in other studies (Adler-Leavy et al., 2007; Bamberg et al., 2012; Chi-Hong Ho et al., 2005; Domingues et al., 2014; Huang et al., 2006; Nasser et al., 2003; & Zaib-un-Nisa et al., 2003) where the mothers of twins in the MAR group underwent cesarean deliveries more frequently than the mothers in the SC group. The observed increase in the incidence of cesarean sections in the MAR group could be attributed to the mother's and physician's concerns regarding pregnancy outcome rather than obstetric indications. In addition, woman conceived by MAR have more concern for their babies, owed to difficulties encountered during conception. For triplet pregnancies, the gynecologists in the studied hospitals operated cesarean section for all triplets except for two mothers who delivered vaginally due to presence of active labor. Studies showed that performing the cesarean section for the HOM pregnancies decreased the incidence of perinatal morbidity and mortality (Feingold et al., 1988; Umeora et al., 2011). Our findings are consistent with findings in studies of Fennessy et al, and Ipitiz et al. in which the majority of triplets were delivered by cesarean section without any difference between SC and ART group. In our study, we also found no difference between groups with regards to the incidence of postpartum hemorrhage. It is worthwhile noting that the incidence of postpartum hemorrhage occurred more frequently for the mothers delivered in the public hospitals.

Regarding the maternal and obstetric results according to the type of MAR, most of the prior studies failed to make any clear mention of the IVF, IUI, and IOO categories, whereas some studies grouped IVF and IOO with spontaneous conception and this was in particular for twin pregnancies, the available literature is lacking for comparisons between these group for triplet pregnancies. In this study, we made a difference when we evaluated

the maternal outcomes for twin and triplet births according to the types of MAR (IVF, IUI, and IOO).

This study demonstrates that the women with twins in the IOO group reflected less infertility rate as compared with those in the IUI and IVF (36.3% vs. 71.4% of the IUI vs. 99.0% of the IVF). Our findings were not in line with Dominguez et al. (2014) study which showed that 85% of the women in the IOO group had a history of infertility. This result may confirm the observation of the experts about the use of the IOO for non-medical purposes; selection of male gender is one of these purposes. Couples who seek MAR should be directed towards the suitable selection of the MAR technique with the presence of medical and non-medical reasons. Also, those couples should be informed about the pregnancy outcomes as a result of using these techniques.

Our study further showed that the IOO-treated women had less use of cervical stitch, gave births in public hospitals, and they were less likely to have complications by preterm delivery and to have delivery by cesarean section than other groups. It is possible that the IOO-treated women haven't had very high expectations of the pregnancy outcomes than mothers in the IVF and IUI group where there were higher infertility rates in these groups. Moreover, the IOO-treated women were more likely to report living in south WB which may reveal the differences in clinical practices in these countries. We also found that the history of abortion was less common in the IVF group. The IUI-treated women with twins were more educated and employed, more likely to report living in middle WB. They had higher prevalence of hypertensive complications and they had less prevalence of fetal-malpresentation. Our findings were not consistent with Huang et al. (2006) findings where the incidence of pregnancy-induced hypertension was similar between SC, IUI and IVF/ICSI group. The observed increase in the prevalence of hypertensive complications among the IUI treated women could be attributed to limited population size, and therefore suggest that further research will be required by extending the number of observations to further verify the current data.

Compared with other studies, our results shared a number of similarities with Huang et al.'s findings where they found higher cesarean delivery in IUI and IVF group. Our findings were not consistent with Chi-Hong Ho et al.'s (2005) and Olivvenes et al.'s (1996) findings, who compared the pregnancy outcomes of twin pregnancies resulted from IVF, IOO, and after spontaneous conception and found no significant differences between groups. Putterman et al.'s (2003) compared the outcomes of twin pregnancies after IVF, IOO with spontaneously conceived twins and found bad obstetric history noted in women in the IOO group. Domingues et al.'s (2014) found no difference in pregnancy outcomes between study subgroups. Huang et al.'s (2006) found that the incidence of PROM was lower in the IUI group compared with spontaneous conception and IVF/ICSI group and finally Dominguez et al.'s findings where the results were independent of the induced methods, except for mother's age where the IOO-treated women were associated with younger maternal ages, and they were associated with lower rates of puerperal complications.

As far as literature on maternal and obstetrical outcomes of triplets' pregnancy after IVF, IUI, and IOO conception is found to be scarce, these outcomes are obtained in our study. The IOO was associated with younger maternal ages, less infertility, and the deliveries were less likely to occur in public hospitals. The IVF-treated women more frequently performed cervical stitch. The IUI-treated women with triplets were more likely to report living in north WB, more likely to be with no previous births, and they were more likely to have PPRM. Given that our findings are based on a limited number of populations, these results call for further research, by extending the number of observations

#### **5.4 Neonatal outcomes of multiple births according to the method of conception (SC, MAR) and to the type of MAR (IVF, IUI and IOO)**

In Multiple births, it is well known that the most common complications are preterm delivery and low birth weight of (<2500 g) because with increasing the number of fetuses, duration of the pregnancy decreases and the growth of fetuses will be affected (ASRM, 2012). Prevention of prematurity is difficult when it is due to high order multiple pregnancies in spite of recent advanced knowledge and research in this field (Nasseri & Azhir, 2009). The biggest concern with premature newborns is the lack of development of the newborn's lung, brain, circulatory system, intestinal system, and eyes (ASRM, 2012). Moreover, later in life, these babies are at greater risk for developmental problems and cerebral palsy (Nasseri and Azhir, 2009). The mean gestational age of our population which was (36.0 weeks, SD 2.9 for twins), (32.2 weeks, SD 2.8 for triplets), and (32.0 weeks, SD 0.9 weeks for quadruplets) is comparable to the mean reported by the (ASRM, 2012), in which the average duration is 35 weeks for twins, 32 weeks for triplets, and 30 weeks for quadruplets.

Furthermore, multiple birth neonates with low birth weight consequently are a result of the lower length of gestation or because sharing two or more newborns for the same placenta may affect the growth of the newborns (ASRM, 2012). Singletons weigh an average of 3,300 g at 38.6 weeks of gestation, twins weigh 2,300 g at 35 weeks, triplets weigh 1,660 g at 32 weeks, and quadruplets weigh 1,300 g at 30 weeks (ASRM, 2012). Comparing our results with this data showed consistency, where the mean birth weight for twins was (2370.3 g, SD 584.5), (1608.5 g, SD 476.9) for triplets and (1480.1 g, SD 242.4) for quadruplets.

The findings of the present study also corroborate the extensive evidence that the multiple birth neonates had higher incidence of prematurity, birth weight <2,500 g, discordance in birth weight, the need for admission to the NICU, and respiratory problems (Adamson & Baker, 2004). In the recent study, the medically assisted conceived twins were more likely to have lower mean gestational age, lower mean birth weight, higher incidence of prematurity, more neonates with birth weight <2,500 g, lower apgar scores at one minute of delivery, and higher incidence of respiratory problems. Also, in the medically assisted twin group, there were more neonates that needed phototherapy, and NICU admission with longer hospital stay. The findings were consistent with the results from Zuppa et al. (2001) study which found that the neonatal outcomes in terms of premature births, low birth

weight, major neonatal diseases, respiratory diseases and severe depression at birth were higher among twins in the MAR group.

Also, our results confirm the results of Nasser et al. (2003) study who found that the neonates resulting from IVF were at higher risk for low birth weight, with higher incidence of admission to NICU, respiratory distress syndrome. In addition to the results from Daniel et al. (2000) study that showed that the ART twin neonates had higher incidence of low mean birth weight and more neonates both first and second who needed admission to NICU. Also, Narine et al. (2003) found earlier gestational age, higher rate of low birth weight in the induced twin group, whereas they found no difference in the birth weight discordance between groups. Also, our results agree with the results of Domingues et al.'s (2014) study who found no significant difference in the incidence of malformation and birth weight discordance, and with Chi-Hong Ho et al. (2005) study who found comparable result with regarding to birth weight discordance, and with Adler –Leavy et al. (2007) who found lower gestational age in the IVF group.

But our findings did not agree with those from Anbazhagan et al. (2014) study who studied 1504 twins, resulted from spontaneous and 466 twin resulted from medically assisted conception and found no significant differences in the outcomes in both groups even after adjustment for chorionicity, maternal age, parity, gestational age, or those from Chi-Hong Ho et al. (2005) study who found higher risk of neonatal complications in spontaneous twin group and similar perinatal outcomes after excluding the mono chorionicity births, or those from Huang et al study who found similar outcomes between groups. Domingues et al. (2014) also found no difference in the incidence of NICU admission between groups, or those in the Putterman study who found similar neonatal outcomes among study groups of (IVF, IOO, and spontaneous conception group).

In the present study the observed increase in the neonatal complications in the medically assisted conceived twin group could be interpreted as being a result of the higher incidence of preterm delivery in this group. After stratification, neonatal complications by gestational age, and birth weight, the highest risk of complications was found among the neonates with lower gestational age, and lower birth weight. We also found that the cesarean delivery was associated with lower apgar score readings at one minute of delivery in this group. Chorionicity is also one of the most important factors that may affect the neonatal outcomes (Bamberg et al., 2012). Unfortunately, this issue was poorly documented in our study group. But it is well approved that the neonates with Dichorionic placenta have better outcomes than those with monochorionic placenta (Daniel et al., 2000).

Many studies also indicated that the medically assisted conceived twins are mostly dichorionic. (Bamberg et al., 2012) found that 96.7% of the induced twins were dichorionic twins in comparison with 75.8% in the spontaneous group, and the frequency of mono chorionicity in twins after ART is only 3% to 7% compared with 26% in spontaneously conceived twins. As well as in Anbazhagan et al. (2014) study who found that the incidence of dichorionicity was 97% of the medically assisted conception group compared with 74% of the spontaneous conception group. So, it is expected to have better

outcomes among the medically assisted conception group. Concerning this matter, it would be helpful to determine chorionicity of multiple births as monochorionic twins and dichorionic triplets because they have a significantly higher morbidity and mortality.

As is well known, higher-order multiple births are rare; consequently, studies about the neonatal outcomes after spontaneous and medically assisted conception are very limited. Furthermore, the available studies in the literature showed inconclusive results, due to the small number of populations that were analyzed.

The current study revealed similar mean gestational age and birth weight in both groups of triplets, but unlike other studies carried out in this area, we found an increase prevalence of mild birth weight discordance (15-25%), apgar score <7 at one minute of delivery, respiratory disorders, hematologic problems, the need for phototherapy in the MAR group. Also, the triplet neonates in the MAR group had longer hospital stay. The observed increase might be explained by higher premature delivery <32 weeks and birth weight <1500 g in this group. Our results have similarities with Zuppa et al. 's (2007) findings of similar mean gestational age and mean birth weight between groups, insignificant difference in the incidence of birth weight discordance of  $\geq 25\%$ , lower Apgar score at 5 minutes of delivery, and sepsis. Similarities were also observed in Friedler et al.'s (1994) findings when they showed no difference between groups in the incidence of low birth weight. Our findings are in contradiction with Fitzsimons et al.'s (1998) who found no significant difference in perinatal and neonatal morbidity in triplet newborns after spontaneous and medically assisted conception group, Zuppa et al.'s (2007) study which showed insignificant difference between groups in the incidence of lower apgar score at one minute of delivery, and respiratory complications, in addition to comparable percentages of gestational age and birth weight after stratification them. Finally, they were in contradiction as well with Friedler et al. 's (1994) when they reported lower mean gestational age in the medically assisted group; and higher percentage of very low birth weight.

Regarding perinatal and neonatal mortality, it was found that there was no difference between study groups of twins. This is consistent with the findings from Anbazghan et al. (2014) and with Huang et al. (2006) study. Our findings are in contradiction with findings in the Chi-Hong Ho et al.'s (2005) study who found that the perinatal mortality was higher in the SC group which was due to chorionicity, where the monochorionic rate was higher in the spontaneous group, and with the findings in the Daniel et al.'s (2000) study who found that the neonatal death rate was comparable between ART group and the ovulation induction and spontaneous group, but it was more frequently found among the second twin in ART group when taken as a whole. The perinatal and neonatal mortality rate was slightly higher in the SC group of triplets. Our findings were consistent with those in the study of Fennesy et al. (2015) who found a comparable neonatal death rate between ART and spontaneous conception. The perinatal and neonatal mortality rate was higher among triplet neonates resulted from IOO treatment, our finding was not consistent with those in the study of Friedler et al. (1994) who found no difference in perinatal mortality rate in the three groups of ART, ovulation induction by clomiphene citrate, ovulation induction by

gonadotropin and the spontaneous conception, and with Lipitiz et al. (1993) who found no significant difference in the neonatal mortality in ovulation induction, IVF, and spontaneous group. Incomplete data about causes of death limited further analysis. But it is well known that the most important factors that determine neonatal mortality of multiple births are the prematurity (ASRM, 2012). According to our data, perinatal and neonatal mortality was not affected by mothers' age and parity, whereas it was associated with lower gestational age.

The other assessed parameters were the gender of neonates, and the sex concordance. This study showed that the rate of male neonates was slightly higher in the MAR group of twins (52.4% of the MAR vs. 50.6% of the SC) and triplets (50.5% of the MAR vs. 46.9% of the SC). This is in good agreement with findings in Chi- Hong Ho et al.'s (2005) study where 52.7%/51.4% of the ART first and second twin neonates were males, as were 61.3%/67.7% of the IOO group. Furthermore, in the MAR group there were more twin neonates with different sex and less neonates with same sex, and the majority of neonates in triplet groups were of different sex. However, the rate was higher in the MAR group, which was expected as women undergoing ART received ovulation induction treatment and the embryos cultured in vitro fertilization. Umero et al.'s (2011) found that among 21 sets of triplets after spontaneous conception only six sets were found with same sex. This is in good agreement with our findings where 3 out of 10 sets in spontaneous group of triplets were found with same sex sets.

The other interesting result from our study is the description of neonatal outcomes of the multiple births of neonates according to the type of MAR. We found that twins in the IOO group had lower rates of premature neonates, and less need for NICU admission, however, they had a longer hospital stay. Also, our study showed that there were more neonates in the IVF group weighing <2,500 g, and a higher number of neonates who had apgar score <7 at one minute of delivery. Twins in the IUI were born one week earlier and slightly lighter compared with those in other groups, and had more sets of different sexualities. The findings from the IUI group thus need to be interpreted with attention due to limited population size. Our results share a number of similarities with Daniel et al. 's (2000) findings where the IVF twin neonates are more likely to be admitted to NICU, and fewer newborns who are found with >2500 g. Dominguez et al. (2014) found that the incidence of NICU admission between IOO, IVF and ICSI group was comparable. Our results do not support their findings.

Among the three groups of triples, IUI and IOO neonates were slightly lighter. IVF neonates had a higher need for phototherapy. The neonates following IOO treatment had higher apgar scores of <7 at 5 minutes and appear to have higher perinatal and neonatal mortality rate. In addition, there were more male neonates in this group. Neonates following IUI treatment born one week earlier, more neonates weighed <1,500 g, and fewer weighed between 1,500 to 2,500 g, more had hematologic problems, and had a longer hospital stay. Furthermore, triplets in the IUI group had more neonates of different sex sets. The findings from the IUI group thus also need to be interpreted with attention due to limited population size

Our results have a number of similarities with Lipitiz et al.'s (1993) study when they compared 99 triplet pregnancies (16 after clomiphene citrate, 56 after menotropin ovulation induction, and 27 as a result of IVF) with those of seven spontaneous triplet pregnancies and found little effect of methods of conception on the gestational and birth weight and no significant difference in neonatal complications including respiratory distress syndrome, intra ventricular hemorrhage, neonatal sepsis, and necrotizing enterocolitis.

### **Summary**

In this study, multiple births constitute 2.2% of all births. Although this prevalence was in line and sometimes lower than the prevalence in other countries, each taken as a whole, the prevalence of twin births was lower than that in other studies, while the prevalence of higher-order multiple births was higher compared with other studies. According to methods of multiple births conception, the prevalence of twins and triplets after spontaneous conception was nearly comparable with prevalence in other studies. The prevalence of twins conceived by MAR was nearly comparable with other studies, whereas the prevalence of higher-order multiple births was higher than that in other studies. When comparing mothers' characteristics, similarities and differences exist. Factors affecting mother's choices in the medically assisted conception group were similar in general with factors found in other studies, despite differences in the prevalence of infertility and parity in this group when compared with other studies. Our results also have a number of similarities and differences in the incidence of maternal, obstetrical and neonatal complications associated with multiple pregnancies. But we are in good agreement with many studies with higher prevalence of preterm delivery and the resulting complications for the neonates as well as the higher prevalence of operative delivery in the MAR group. Like many other previous researches, our study plays an important role in emphasizing preventive interventions not only restricted to higher-order multiple births, but should also include twins.

## Chapter six

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### Conclusion and recommendations

#### 6.1 Conclusions

This study adds to the growing pool of evidence regarding the outcome of multiple births depending on method of conception. The noticeable alarming rate of multiple births and the lack of studies regarding this matter in the west bank, this study was conducted to determine its prevalence, methods of conception and its health consequences on the mothers and babies in five selected hospitals during the period of two years (2010-2011). This study demonstrated that 2.2% of all births were multiple births, which is parallel to other studies. Close monitoring for the incidence of these births is the need to monitor the increase in its prevalence.

While multiple births are a relatively rare phenomenon, it has become more common in recent years due mainly to the more widespread use of fertility drugs and assisted reproduction techniques. In this study, 31.7% of twins and 83.7% of the higher-order multiple births were due to medical assisted reproduction. IVF and fertility drugs were more frequently used. In this study, Infertility and lower parity can influence the decision whether to use the MAR for conception. With the increasing affordability of fertility treatments and with more frequent turnout to use the fertility drugs because it is cheaper and easier to use, may increase the state-specific multiple births rate. So, policies and treatments practices to reduce the incidence of multiple pregnancies on ovulation induction and ART can be targeted and these treatments should be used by the specialists to prevent overusing them. Also, well-constructed trials demonstrate that higher-order multiple births can be reduced or eliminated without compromising a couple's chances to conceive.

Multiple pregnancies, deliveries, and multiple birth infants require close monitoring and care due to the associated risks, and there is an immediate need for efforts to reduce the adverse perinatal outcomes. Because the primary prevention of the risks associated with multiple pregnancies such as prematurity are often unattainable, mothers with multiple gestations should seek increased obstetric care. According to the results of this study, the use of MAR in twin pregnancy, preterm delivery is more frequent; cesarean section is usually the method of delivery for these patients. The infertility treatment triplet pregnancies, whatever the technique was, were not at increased risk for obstetric

complications. Our study suggests that the mothers in the SC group were at higher risk for hypertensive complications and anemia. This finding requires further confirmation

The risk of neonatal complications among twins including lower mean gestational age and mean birth weight, respiratory disorders, apgar score <7 at one minute of delivery, hematologic problems, the need for phototherapy, NICU admission, and the duration of NICU admission were also higher in the medically assisted conception group. Among triplets, our study also suggests that when the MAR was used the incidence of respiratory problems, hematologic problems, apgar score <7 at one minute of delivery, and the need for phototherapy increased and the duration of hospital stay was longer for neonates.

The use of IOO for conception has a better outcome on twin pregnancy outcomes in terms of lower incidence of preterm delivery and cesarean delivery, also neonates have lower need for NICU admission, however this type of medically assisted conception was associated with lower apgar score (apgar score <7) at five minutes of delivery, and higher perinatal and neonatal mortality rate among neonates of triplets. When IVF is used, twin neonates born with birth weight <2,500g, and the apgar score <7 at one minute of delivery increased and triplet neonates who used phototherapy increased as well.

Our results do not allow us to draw definitive conclusions concerning the consequences of IUI treatment for maternal, obstetrical and neonatal outcomes in twin and triplet pregnancies. Nevertheless, our study provides useful indications for further research, by extending the number of observations of major obstetric morbidity; in particular of hypertensive complications for twin pregnancy, and PPRM for triplet pregnancies, and neonatal morbidity; in particular lower gestational age for twin and triplet pregnancy, and the associated consequences of on birth weight, longer hospital stay and increase the incidence of hematologic problems among the neonates of triplets.

Both obstetric and neonatal outcomes must be considered in medically assisted conceived multiple pregnancies. So that reducing the multiple birth rates following medical assisted conception treatments remains the priority.

## **6.2 Recommendations**

### **Recommendations for the reproductive specialists who are working in infertility clinics:**

To make the MAR the standard of care in the treatment of infertility, we recommend the following:

- Limiting the number of embryos that can be transferred to avoid increasing the higher incidence of HOM births in the future because the fetal reduction is not the optimal or desirable approach to dealing with multiple pregnancies because this procedure is ethically unacceptable for almost all cases.
- To reduce the risks of multiple pregnancies associated with ART and to optimize pregnancy rate, national guidelines should be developed regarding the number of

embryos replaced according to characteristics such as patients' age and embryo grade.

- All reproductive specialists need to be knowledgeable about the very real increased risks and costs of multiple pregnancies for the woman, the babies, and their family. They should be aware of the ethical and social issues as well.
- A significant risk of MAR is multiple pregnancies. Infertile couples need to be informed about the increased risk of multiple pregnancies.
- The resulting complications of the MAR can be used in counseling patients with triplet and quadruplet pregnancies.
- For couples considering the MAR for fetal gender selection, those should be advised for using the appropriate techniques.

#### **Recommendations for the Gynecologists who are working in the hospitals:**

- The clinicians should pay more attention to multiple births chorionicity versus the mode of conception because the mono chorionicity might be the most confounding factor when comparing twin pregnancies between both groups MAR and spontaneous conception.
- For every woman requesting cesarean delivery, the responsible obstetricians should discuss the risks and benefits of planned vaginal delivery and cesarean section.

#### **Recommendations for the decision makers:**

- Improving access to care through more financial support and insurance might reduce some of the pressure from patients to replace more embryos.
- Trying to establish governmental infertility treatment clinics to make more observations and to keep on responsible practices.
- Follow up monitoring medically assisted reproduction and make sure that this type of reproduction is used for medical indications only.
- The reproductive specialists should continue to raise awareness regarding reproductive health programs, taking advantage of the appropriate age to be fertile.
- Promote the pregnant mothers to keep following up with the hospital they want to deliver in to have a history record in the hospital that are necessary for delivery.

#### **Recommendations for future research**

Multiple births are a more complex issue that requires further studies.

- Research is needed in the areas of the reduction of multiple births rates through fertility treatments.

- Follow up studies also are needed to monitor the long- term health problems of multiple births.
- Studies that examine the economic implications (frequency, duration, and cost of hospital admissions), and to examine the contribution of MAR to the incidence and cost of multiple births.
- Further research is required to clarify the contribution of infertility itself to adverse obstetrical and perinatal outcomes.
- Study to evaluate the contribution of multiple births to preterm delivery and low birth weight for all the population should be conducted.
- Further research into the psychosocial impact of MAR is needed.
- Further research is required to study the relationship between the preterm delivery and the use of the cervical stitch.
- There is a need for more clinical studies. Also, there is a need for reports from the ART clinics that showed the success rate and pregnancy outcomes as a result of using these techniques.

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## Annexes

### Annex 1 Experts who validated the study instrument

<b>Name</b>	<b>Qualification</b>
Dr. Sumaya Sayej	Thesis advisor
Dr. Sudqui Hamadah	Neonatologist
Dr. Ahmad Abo Khaizaran	Obstetrician
Dr. Imad Abed	Obstetrician

## Annex 2 Study questionnaire

Part One/ Mother's File	
1.1 Identification Information	
<input type="checkbox"/>	<b>Q1. Place of residence:</b> 1. South 2. Center 3. North
<input type="checkbox"/>	<b>Q2. Type of hospital:</b> 1. Governmental 2. Private
<input type="checkbox"/>	<b>Q3. Name of hospital:</b> 1. Alia 2. Palestinian Medical Complex 3. Red Crescent 4. Rafidia 5. Specialized Arab Hospital
<input type="checkbox"/>	<b>Q4. Hospital record number:</b> .....
	<b>Q5. Admission Date:</b> ..... / ..... / .....
1.2 Socio-demographic Data	
<input type="checkbox"/>	<b>Q6. Mother's age (Years):</b> .....
<input type="checkbox"/>	<b>Q7. Mother's Education:</b> 1. Unknown 2. Illiterate 3. Elementary 4. Preparatory 5. Secondary 6. Associate diploma 7. Bachelor and above
<input type="checkbox"/>	<b>Q8. Mother's Occupation:</b> .....
<input type="checkbox"/>	<b>Q9. Husband's Education:</b> 1. Unknown 2. Illiterate 3. Elementary 4. Preparatory 5. Secondary 6. Associate diploma 7. Bachelor and above
<input type="checkbox"/>	<b>Q10. Husband's Occupation:</b> .....
<input type="checkbox"/>	<b>Q11. Consanguinity:</b> 1. Unknown 2. First cousin 3. Second cousin 4. Distant relative 5. Not related
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<b>Q12. Family monthly income:</b> .....
1.3 Health History	
<input type="checkbox"/>	<b>Q13. Mother's blood type:</b> 1. Unknown 2. A+ 3. A- 4. B+ 5. B- 6. AB+ 7. AB- 8. O+ 9. O- 10. Rhesus negative 11. Rhesus positive
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<b>Q14. Mother's Body Mass Index:</b> Height (cm): ..... Weight (kg): .....

<input type="checkbox"/>	<b>Q15.Smoker:</b> 1. Unknown 2. Yes 3. No
<input type="checkbox"/>	<b>Q16. If she is smoker, is she:</b> 1. Active 2. Passive
<input type="checkbox"/>	<b>Q17. Previous medical history:</b> 1. Unknown 2. No 3. Yes: .....
<input type="checkbox"/>	<b>Q18. Previous surgical history:</b> 1. Unknown 2. No 3. Yes: .....
<input type="checkbox"/>	<b>Q19.Exposure to oral contraceptive before last pregnancy:</b> 1. Unknown 2. Yes 3. No
<input type="checkbox"/>	<b>Q20.If yes, duration of cessation (months):</b> .....
<input type="checkbox"/>	<b>Q21.Obstetric History:</b> Para: .....
<input type="checkbox"/>	Gravid: .....
<input type="checkbox"/>	Abortion: .....
<input type="checkbox"/>	<b>Q22. Previous history of multiple births:</b> 1. Unknown 2. No 3. Yes (number): .....
<input type="checkbox"/>	<b>Q23. If yes, mode of conception in multiple births:</b> 1. Unknown 2. Spontaneous 3. Assisted (type: 1. IVF 2. IUI 3. Drug stimulation)
<input type="checkbox"/>	<b>Q24. Family history of multiple births:</b> 1. Unknown 2. No 3. Yes (who): .....
<b>1.4 Last pregnancy variables</b>	
<input type="checkbox"/>	<b>Q25. Date of last menstrual period (LMP):</b> ..... /...../.....
<input type="checkbox"/>	<b>Q26. Mode of conception:</b> 1. Spontaneous conception ( <b>Skip to Q32</b> ) 2. Medical assisted conception (infertility) 3. Medical assisted conception (no infertility) (why?): ..... ( <b>Skip to Q30</b> ) 4. Medical assisted conception (unspecified) ( <b>Skip to Q30</b> ) 5. Unspecified ( <b>Skip to Q32</b> )
<input type="checkbox"/>	<b>Q27.If the answer in the previous question is 2, what is the duration of infertility in years?</b> .....
<input type="checkbox"/>	<b>Q28.Type of infertility:</b> 1. Unknown 2. Primary 3. Secondary
<input type="checkbox"/>	<b>Q29. Causes of infertility:</b> 1. Unknown (Minimal response: 1. Yes 2. No) 2. Male infertility: (Type) ..... 3. Female infertility: (Type) ..... 4. Unexplained infertility

<input type="checkbox"/>	<b>Q30. Type and Number of Assisted reproductions:</b> 1. IVF ( )                      2. IUI ( )                      3. Drug stimulation ( )
<input type="checkbox"/>	<b>Q31. Number of Fetuses inserted (In case of IVF):</b> .....
<input type="checkbox"/>	<b>Q32. Fetus reduction(selective reduction):</b> 1. Unknown                      2. Yes :( Number) .....                      3. No
<input type="checkbox"/>	<b>Q33. Vanishing twin:</b> 1. Unknown                      2. Yes :( Number) .....                      3. No
<input type="checkbox"/>	<b>Q34. Pregnancy outcomes:</b> 1. Twins                      2. Triplet                      3. Quadruplets                      4. $\geq$ Quintuplets.....
<input type="checkbox"/>	<b>Q35. Complications during pregnancy:</b> 2. 1. Unknown                      2. No                      3. Yes :( type) .....
<b>1.5 Antenatal care:</b>	
<input type="checkbox"/>	<b>Q36. Antenatal visit:</b> 1. Unknown    2. Began at (1-3) months    3. Began at (4-6) months    4. Began at (7-9) months 5. No visits
<input type="checkbox"/>	<b>Q37. Corticosteroids injections during pregnancy:</b> 1. Unknown                      2. No                      3. Yes :( Months, Doses) .....
<input type="checkbox"/>	<b>Q38. Hormonal supplement during pregnancy:</b> 1. Unknown                      2. No                      3. Yes: (type) .....
<input type="checkbox"/>	<b>Q39. Detailed ultrasound:</b> 1. Unknown                      2. No                      3. Yes: (Months/Result) .....
<input type="checkbox"/>	<b>Q40. Triple test (for certain congenital defects):</b> 1. Unknown                      2. No                      3. Yes: (Months/Result) .....
<b>1.6 Delivery variables:</b>	
<input type="checkbox"/>	<b>Q41. Type of Labor:</b> 1. Unknown    2. Spontaneous    3. Induced 4. Augmented 5. No labor ( <b>Skip to Q 43</b> )

<input type="checkbox"/>	<b>Q42. Duration of labor:</b> .....
<input type="checkbox"/>	<b>Q43. Rupture of membrane (ROM):</b> 1. Unknown 2. SROM 3. PROM 4. PPRM 5 AROM (Time of rupture prior to deliver(:.....
<input type="checkbox"/>	<b>Q44. Complications during delivery:</b> 1. Unknown 2. No 3. Yes: (type): .....
	<b>Q45. Delivery date.... /..... /.....</b>
<input type="checkbox"/>	<b>Q46. Delivery time.....</b>
<input type="checkbox"/>	<b>Q47. Delivery mode:</b> 1. Unknown 2. Vaginal delivery 3. Instrumental 4. Cesarean section C/S 5. Others/ specify:.....
<input type="checkbox"/>	<b>Q48. If it was instrumental:</b> 1. Unknown 2. Forceps 3. Vacuum 4. Both
<input type="checkbox"/>	<b>Q49. If it was Cesarean SectionC/S:</b> 1. Unknown 2. Elective 3. Emergency: (Cause).....
<input type="checkbox"/>	<b>Q50. Complications for the mother after delivery:</b> 1. Unknown 2. No 3. Yes: (type) .....

**Part two/Newborns File**

**2.1 Newborns Information**

<input type="checkbox"/>	<b>Q51. Gestational age at delivery (Weeks):</b> .....						
No. of NB	Gender 1. M 2. F	Birth weight (gm)	Blood Group 1. A+2. A- 3. B+ 4. B- 5. AB+6.AB- 7. O+ 8. O- 9. Rhesus negative 10. Rhesus positive 11. Unknown	Apgar score at		Fetal presentation 1. Cephalic 2. Breach-complete 3. Breach-foot 4. Transverse 5. Unknown	Chorionicity
				1min	5mins		
1	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	..... ..... .....
2	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	..... ..... .....
3	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	..... ..... .....
4	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	..... ..... .....

5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	..... ..... .....
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2.2 Newborns' complications										
No. of NB	Newborn's Complications	Types of complications			Length of hospital stay (days)	Re-admission	Newborn's Outcomes	abnormality	If there was abnormality	Details
0. Missing file 10. IUFD 30. still birth	1. Yes 2. No 3. Unknown				0. Less than one day 99. Unknown	1. Yes 2. No 3. unknown	1. Died 2. Alive 3. Unknown	1. Yes 2. No 3. Unknown	1. Major 2. Minor 3. unknown	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### Annex 3 Socio-demographic characteristics of the triplets' and quadruplets' mothers

Parameters	Triplets	Quadruplets
<b>Maternal age</b>	<b>N=81</b>	<b>N=6</b>
Mean (SD)	27.9 (4.9)	27.8 (5.5)
Minimum-maximum	19-39	22-35
<20	2 (2.5%)	—
20-24	20 (24.7%)	3 (50.0%)
25-29	31 (38.3%)	—
30-34	18 (22.2%)	2(33.3%)
35-39	10 (12.3%)	1 (16.7%)
40-45		—
<b>Mother's education</b>	<b>N=65</b>	<b>N=6</b>
Basic	15 (23.1%)	2 (33.3%)
Secondary	22 (33.8%)	3 (50.0%)
Higher	28 (43.1%)	1 (16.7%)
<b>Mother's work status</b>	<b>N=68</b>	<b>N=6</b>
House wife	55 (80.8%)	5 (83.3%)
Employed	11 (16.2%)	1 (16.7%)
Student	2 (2.9%)	—
<b>Consanguinity</b>	<b>N=64</b>	<b>N=6</b>
Relative	16 (25.0%)	2 (33.3%)
Not relative	48 (75.0%)	4 (66.7%)
<b>Place of residence (WB)</b>	<b>N=82</b>	<b>N=6</b>
South	23 (28.0%)	2 (33.3%)
Center	15 (18.3%)	—
North	44 (53.7%)	4 (66.7%)
<b>Type of hospital</b>	<b>N=82</b>	<b>N=6</b>
Public	44 (53.7%)	2 (33.3%)
Private	38 (46.3%)	4 (66.7%)

Note.

WB: West Bank

#### Annex 4 Medical and obstetrical histories of the triplets' and quadruplets' mothers

Parameters	Triplets	Quadruplets
<b>Medical history</b>	<b>N=73</b>	<b>N=6</b>
Yes	5 (6.8%)	1 (16.7%)
No	68 (93.2%)	5 (83.3%)
<b>Cervical stitch</b>	<b>N=72</b>	<b>N=6</b>
Yes	51 (70.8%)	4 (66.7%)
No	21(29.2%)	2 (33.3%)
<b>Parity</b>	<b>N=81</b>	<b>N=6</b>
0	42 (51.9%)	2 (33.3%)
1	18 (22.2%)	1 (16.7%)
≥2	21 (25.9%)	3 (50.0%)
<b>Previous abortion</b>	<b>N=81</b>	<b>N=6</b>
Yes	19 (23.5%)	1 (16.7%)
No	62 (76.5%)	5 (83.3%)
<b>Previous history of multiple births</b>	<b>N=67</b>	<b>N=6</b>
Yes	9 (13.4%)	—
No	58 (86.6%)	6 (100.0%)
<b>Family History of multiple births</b>	<b>N=63</b>	<b>N=6</b>
Yes	44 (69.8%)	4 (66.7%)
No	19 (30.2%)	2 (33.3%)
<b>Infertility history</b>	<b>N=66</b>	<b>N=6</b>
Yes	45 (68.2%)	4 (66.7%)
No	21 (31.8%)	2 (33.3%)

**Annex 5 Medical history of the multiple birth mothers for the overall groups and according to the method of conception**

Medical diseases	Twins					
	Mode of conception					
	Total	SC	MAR			
	N=755	Total N=478	Total N=214	IVF N=104	IUI N=8	IOO N=102
<b>Respiratory</b>						
Plural effusion	2 (0.3%)	2 (0.4%)	—	—	—	—
Asthma	8 (1.05%)	4 (0.8%)	4 (1.9%)	3 (2.9%)	—	1 (1.0%)
<b>Hepatic</b>						
Hepatitis antigen positive	4 (0.5%)	3 (0.6%)	1 (0.5%)	—	—	1 (1.0%)
Hepatitis	1 (0.1%)	—	1 (0.5%)	1 (1.0%)	—	—
Hepatitis B virus carrier	1 (0.1%)	1 (0.2%)	—	—	—	—
liver cirrhosis	1 (0.1%)	1 (0.2%)	—	—	—	—
<b>Endocrine</b>						
Hypothyroidism	7 (0.9%)	5 (1.04%)	2 (0.9%)	—	—	2 (1.96%)
Diabetes mellitus	5 (0.6%)	4 (0.8%)	1 (0.5%)	1 (1.0%)	—	—
<b>Heart</b>						
Grade 3 ejection systolic murmur	1 (0.1%)	1 (0.2%)	—	—	—	—
Heart disease	1 (0.1%)	—	1 (0.5%)	—	—	1 (1.0%)
<b>Hypertension</b>	5 (0.7%)	4 (0.8%)	1 (0.5%)	—	—	1 (1.0%)
<b>Depression</b>	1 (0.1%)	—	1 (0.5%)	1 (1.0%)	—	—
<b>Rheumatoid arthritis</b>	3 (0.4%)	2 (0.4%)	1 (0.5%)	1 (1.0%)	—	—
<b>Thalassemia</b>	4 (0.5%)	1 (0.2%)	2 (0.9%)	—	1 (12.5%)	1 (1.0%)
<b>Poliomyelitis</b>	1 (0.1%)	1 (0.2%)	—	—	—	—
<b>Others</b>						
Varicose vein	11 (1.4%)	5 (1.04%)	3 (1.4%)	—	—	3 (2.9%)
Frozen pelvis †	1 (0.1%)	—	—	—	—	—
Allergy to penicillin	2 (0.4%)	1 (0.2%)	1 (4.3%)	1 (1.0%)	—	—
Adhesion between bowel and uterine wall	1 (0.1%)	1 (0.2%)	—	—	—	—
Gall bladder stone	2 (0.3%)	—	2 (8.7%)	1 (1.0%)	—	1 (1.0%)
Allergic bronchitis	1 (0.1%)	—	1 (4.3%)	1 (1.0%)	—	—

Allergy to anesthetics drugs	1 (0.1%)	—	1 (4.3%)	1 (1.0%)	—	—
<b>Triples</b>						
	<b>Total n=73</b>	<b>N=11</b>	<b>N=57</b>	<b>N=42</b>	<b>N=5</b>	<b>N=11</b>
Heart	1 (1.4%)	1 (9.0%)	—	—	—	—
Thalassaemia	1 (1.4%)	—	1 (1.8%)	1 (2.4%)	—	—
Varicose vein	1 (1.4%)	—	1 (1.8%)	—	—	1 (9.1%)
Allergy	1 (1.4%)	—	1 (1.8%)	1 (2.4%)	—	—
<b>Quadruplets</b>						
	<b>Total n=6</b>	<b>N= 2</b>	<b>N=4</b>	<b>N=1</b>		<b>N=3</b>
Varicose vein	1 (16.7%)	1 (50.0%)	—	—		—

*Note.* †missing data about mode of conception.

More than one maternal condition can occur in the same woman.

**Annex 6 Types of hypertensive disorders during pregnancy for the overall groups and according to the method of conception**

Complications	Twins					
	Total	Mode of conception				
		SC	MAR			
	N=765	N=477	Total n=215	IVF n=105	IUI n=8	IOO n=102
Preeclampsia	49 (6.4%)	28 (5.9%)	12 (5.6%)	8 (7.6%)	1 (12.5%)	3 (2.9%)
Pregnancy induced hypertension	21 (2.7%)	8 (1.7%)	11 (5.1%)	6 (5.7%)	2 (25.0%)	3 (2.9%)
HELLP syndrome	3 (0.4%)	1 (0.2%)	2 (0.9%)	2 (1.9%)	—	—
Triplets						
	N=74	N=11	N=58	N=42	N= 5	N= 11
Preeclampsia	4 (5.4%)	2 (18.2%)	2 (3.4%)	1 (2.4%)	—	1 (9.1%)
Pregnancy induced hypertension	1 (1.4%)	—	1 (1.7%)	1 (2.4%)	—	—
Quadruplets						
	N=6	N=2	N=4	N=1	—	N=3
Preeclampsia	3 (50.0%)	1 (50.0%)	2 (50.0%)	—	—	2 (66.7%)

**Annex 7 Types of placental disorders during pregnancy for the overall groups and according to the method of conception**

Complications	Twins					
	Total	Mode of conception				
		SC	MAR			
	N=765	N=477	Total N=215	IVF N=105	IUI N=8	IOO N=102
Abruption placenta	19 (2.5%)	8 (1.7%)	9 (4.7%)	3 (2.9%)	—	6 (5.9%)
Placenta previa	4 (0.5%)	4 (0.8%)	—	—	—	—
Triplets						
	N=74	N=11	N=58	N=42	N=5	N=11
Abruption placenta	2 (2.7%)	—	2 (3.4%)	—	—	2 (18.2%)
Placenta previa	1 (1.4%)	1 (9.1%)	—	—	—	—

**Annex 8 Other maternal and obstetrical complications for the overall groups and according to the method of conception.**

Complications	Twins					
	Total	SC	Mode of conception			
			Total N=215	IVF N=105	IUI N=8	IOO N=102
N=765	N=477					
Unspecified kidney problem	4 (0.5%)	4 (0.8%)	—	—	—	—
Deep vein thrombosis	5 (0.7%)	5 (1.0%)	—	—	—	—
Polyhydramnios §	8 (1.0%)	5 (1.0%)	—	—	—	—
Oligohydramnios	6 (0.8%)	2 (0.4%)	4 (1.9%)	3 (2.9%)	—	1 (1.0%)
Thrombocytopenia	2 (0.3%)	1 (0.2%)	1 (0.5%)	—	—	1 (1.0%)
Hydronephrosis	5 (0.7%)	4 (0.8%)	1 (0.5%)	1 (1.0%)	—	—
Placental calcification	3 (0.4%)	3 (0.6%)	—	—	—	—
Chorioamnionitis	1 (0.1%)	1 (0.2%)	—	—	—	—
Generalized edema	1 (0.1%)	—	1 (0.5%)	1 (1.0%)	—	—
Pancreatitis	1 (0.1%)	1 (0.2%)	—	—	—	—
Cholecystitis	1 (0.1%)	—	1 (0.5%)	1 (1.0%)	—	—
Cholestasis ‡	1 (0.1%)	—	—	—	—	—
Varicose vein	1 (0.1%)	—	1 (0.5%)	—	—	1 (1.0%)
Unspecified liver problem	1 (0.1%)	1 (0.2%)	—	—	—	—
History of preterm labor	9 (1.2%)	5 (1.0%)	4 (1.9%)	3 (2.9%)	1 (12.5%)	—
Chest and back pain	1 (0.1%)	—	1 (0.5%)	—	—	1 (1.0%)
Unspecified abdominal pain	2 (0.3%)	1 (0.2%)	1 (0.5%)	1 (1.0%)	—	—
Triplets						
	N=74	N=11	N=58	N=42	N=5	N=11
Placental calcification	1 (1.4%)	—	1 (1.7%)	1 (2.4%)	—	—
DVT	2 (2.7%)	—	2 (3.4%)	2 (4.8%)	—	—
Oligohydramnios	1 (1.4%)	1 (9.1%)	—	—	—	—
Pyelonephritis	1 (1.4%)	1 (9.1%)	—	—	—	—
Suspected coagulopathy	1 (1.4%)	—	1 (1.7%)	1 (2.4%)	—	—
History of preterm labor	4 (5.4%)	—	4 (6.9%)	2 (4.8%)	—	2 (18.2%)
Unspecified abdominal pain	1 (1.4%)	—	1 (1.7%)	—	1 (20.0%)	—

*Note.*

‡ missing data about mode of conception.

§ missing data about mode of conception for three cases.

## Annex 9 Characteristics of the multiple birth neonates

Parameters	Multiple births			
	Twins	Higher-order multiple births		
		Total	Triplets	Quadruplets
<b>Gestational age (weeks)</b>				
	<b>N=1591</b>	<b>N=262</b>	<b>N=239</b>	<b>N=23</b>
Mean (SD)	36.0 (2.9)	32.2 (2.7)	32.2 (2.8)	32.0 (0.9)
<32	114 (7.2%)	88 (33.6%)	80 (33.5%)	8 (34.8%)
32-36	742 (46.6%)	174 (66.4%)	159 (66.5%)	15 (65.2%)
≥37	735 (46.2%)	—	—	—
<b>Birth weight (gram)</b>				
	<b>N=1582</b>	<b>N=261</b>	<b>N=238</b>	<b>N=23</b>
Mean (SD)	2370.3 (584.5)	1597.3 (462.2)	1608.5 (476.9)	1480.1 (242.4)
<1500	112 (7.1%)	96 (36.7%)	84 (35.3%)	12 (52.2%)
1500-2500	742(46.9%)	158 (60.5%)	147 (61.8%)	11 (47.8%)
≥2500	728 (46.0%)	7 (2.7%)	7 (2.9%)	—
<b>Gender</b>				
	<b>N=1589</b>	<b>N=262</b>	<b>N=239</b>	<b>N=23</b>
Male	818 (51.5%)	131 (50.0%)	117 (49.0%)	14 (60.9%)
Female	771 (48.5%)	131 (50.0%)	122 (51.0%)	9 (39.1%)
<b>Sex concordance</b>				
	<b>N=779</b>	<b>N=82</b>	<b>N=77</b>	<b>N=5</b>
Same sex set	484 (62.1%)	17 (20.7%)	17 (22.1%)	—
Different sex set	295 (37.9%)	65 (79.3%)	60 (77.9%)	5 (100.0%)
<b>Apgar score</b>				
Apgar score at 1 minute				
	<b>N=1567</b>	<b>N=254</b>	<b>N=233</b>	<b>N=23</b>
<7	229 (14.6%)	152 (59.4%)	137 (58.8%)	15 (65.2%)
≥7	1338 (85.4%)	102 (40.6%)	96 (41.2%)	8 (34.8%)
Apgar score at 5 minutes				
	<b>N=1534</b>	<b>N=256</b>	<b>N=233</b>	<b>N=23</b>
<7	68 (4.4%)	40 (15.6)	38 (16.3%)	2 (8.7%)
≥7	1466 (95.6%)	216 (84.4%)	195 (83.7%)	21 (91.3%)

## Annex 10 Birth weight discordance of multiple births for the overall groups

<b>Twins</b>						
<b>Categories</b>	<b>N=779</b>					
<15%	551 (70.7%)					
15-19.9%	93 (12.0%)					
20-24.9%	58 (7.4%)					
≥25	77 (9.9%)					
<b>Triplets</b>						
<b>Categories</b>	<b>Heaviest-lightest N=76</b>	<b>Heaviest-middle N=76</b>	<b>Middle-lightest N=76</b>			
<15%	34 (44.7%)	61(80.3%)	54 (71.1%)			
15-19.9%	10 (13.2%)	6 (7.9%)	7 (9.2%)			
20-24.9%	8 (10.5%)	6 (7.9%)	3 (3.9%)			
≥25	24 (31.6%)	3(3.9%)	12 (15.8%)			
<b>Quadruplets</b>						
<b>Categories</b>	<b>Heaviest- lightest N=5</b>	<b>Heaviest- second N=5</b>	<b>Heaviest- third N=5</b>	<b>Second- lightest N=5</b>	<b>Third- lightest N=5</b>	<b>Second- third N=5</b>
<15%	2 (40.0%)	4 (80.0%)	2 (40.0%)	2 (40.0%)	5 (100.0%)	3 (60.0%)
15-19.9%	—	1 (20.0%)	1 (20.0%)	—	—	1 (20.0%)
20-24.9%	—	—	1 (20.0%)	1 (20.0%)	—	—
≥25	3 (60.0%)	—	1 (20.0%)	2 (40.0%)	—	1 (20.0%)

## Annex 11 Birth weight discordance of multiple births according to the method of conception

<b>Twins</b>						
<b>Categories</b>	<b>Method of conception</b>					
	<b>SCN=464</b>			<b>MARN=214</b>		
<15%	331 (71.3%)			148 (69.2%)		
15-19.9%	51 (11.0%)			27 (12.6%)		
20-24.9%	36 (7.8%)			17 (7.9%)		
≥25	46 (9.9%)			22 (10.3%)		
<b>Triplets</b>						
	<b>SC</b>			<b>MAR</b>		
	<b>Heaviest-lightest N=10</b>	<b>Heaviest-middle N=10</b>	<b>Middle-lightest N=10</b>	<b>Heaviest-lightest N=60</b>	<b>Heaviest-middle N=60</b>	<b>Middle-lightest N=60</b>
<15%	6 (60.0%)	8 (80.0%)	8 (80.0%)	25 (41.7%)	47 (78.3%)	43 (71.7%)
15-19.9%	1 (10.0%)	1 (10.0%)	1 (10.0%)	9 (15.0%)	5 (8.3%)	5 (8.3%)
20-24.9%	—	1 (10.0%)	—	8 (13.3%)	5 (8.3%)	3 (5.0%)
≥25	3 (30.0%)	—	1 (10.0%)	18 (30.0%)	3 (5.0%)	9 (15.0%)

*Note.*

SC, Spontaneous conception; MAR, medical assisted reproduction.

**Annex 12 Neonatal respiratory disorders for the overall groups and according to the method of conception**

Complications	Twins					
	Total	Mode of conception				
		N=1311	SC N=825	MAR-total N=367	IVF N=174	IUI N=15
Respiratory distress syndrome	325 (24.8%)	190 (23.2%)	118 (32.2%)	65 (37.4%)	3 (20.0%)	50 (28.1%)
Transient tachypnea of the newborns	39 (3.0%)	25 (3.0%)	9 (2.5%)	3 (1.7%)	—	6 (4.3%)
Grunting	3 (0.2%)	—	2 (0.5%)	—	2 (13.3%)	—
Bronchiolitis	1 (0.1%)	1 (0.1%)	—	—	—	—
Retraction	2 (0.1%)	—	2 (0.2%)	—	—	2 (1.1%)
Distressed newborns	2 (0.1%)	2(0.2%)	—	—	—	—
Triplets						
	N=184	N=30	N=143	N=101	N=16	N=26
RDS	165 (89.7%)	25 (83.3%)	129 (90.2%)	90(89.1%)	16 (100.0%)	23 (88.5%)
TTN	3 (1.2%)	—	3 (1.6%)	3(2.2%)	—	—
Quadruplets						
	N=18	N=8	N=10	N=3	—	N=7
RDS	16 (88.9%)	8 (100.0%)	8 (80.0%)	3 (100.0%)	—	5 (71.4%)

*Note.*

RDS: respiratory distress syndrome; TTN, transient tachypnea of the newborns.

**Annex 13 Respiratory support in multiple birth neonates with respiratory disorders for the overall groups and according to the method of conception**

Intervention	Twins					
	Total	Mode of conception				
	N=372	SC N=218	MAR-total N=131	IVF N=68	IUI N=5	IOO N=58
Needed mechanical ventilator	66 (17.7%)	35 (16.1%)	27 (20.6%)	11 (16.2%)	1(20.0%)	15 (25.9%)
Needed Surfactant	47 (12.6%)	29 (13.3%)	16 (12.2%)	7 (10.3%)	1(20.0%)	8 (13.8%)
O2 therapy	290(78.0%)	172 (78.9%)	99 (75.6%)	53 (77.9%)	4(80.0%)	42 (72.4%)
Needed CPAP	12 (3.2%)	8(3.7%)	4(3.1%)	3(4.4%)	—	1(1.7%)
Triplets						
	N=168	N=25	N=132	N=93	N=16	N=23
Needed mechanical ventilator	52 (31.0%)	8 (32.0%)	35 (26.5%)	21 (22.6%)	5 (31.3%)	9 (39.1%)
Needed surfactant	35 (20.8%)	5 (20.0%)	25 (18.9%)	15 (16.1%)	4 (25.0%)	6 (26.1%)
O2 therapy	113 (67.3%)	14 (56.0%)	97 (73.5%)	72 (77.4%)	11 (68.8%)	14 (60.9%)
Needed CPAP	2 (1.2%)	—	2 (1.5%)	2 (2.1%)	0(0.0%)	—
Quadruplets						
	N=16	N=8	N=8	N=3	—	N=5
Needed mechanical ventilator	6 (37.5%)	3(37.5%)	3(37.5%)	—	—	3(60.0%)
Needed surfactant	4 (25.0%)	1(12.5%)	3(37.5%)	—	—	3(60.0%)
O2 therapy	10(62.5%)	5(62.5%)	5(62.5%)	3(100.0%)	—	2(40.0%)

*Note.*

CPAP: continuous positive airway pressure.

**Annex 14 Neonatal iatrogenic respiratory disorders for the overall groups and according to the method of conception**

Complications	Twins				
	Total	Mode of conception			
		N=1311	SC N=825	MAR-total N=367	IVF N=174
Pneumothorax	7 (0.5%)	4 (0.5%)	3 (0.8%)	2 (1.1%)	1 (0.6%)
Pulmonary hemorrhage	5 (0.4%)	3 (0.4%)	2 (0.5%)	1 (0.7%)	1 (0.6%)
Interstitial emphysema	1 (0.1%)	1 (0.1%)	—	—	—
Triplets					
	N=184	N=30	N=143	N=101	N=26
Pneumothorax	1 (0.5%)	1 (3.3%)	—	—	—
Pulmonary hemorrhage	6 (3.3%)	—	2 (1.4%)	1(1.0%)	1 (3.8%)
bronchopulmonary dysplasia	1 (0.5%)	—	1 (0.7%)	1 (1.0%)	—
Interstitial emphysema	1 (0.5%)	—	1(0.7%)	1 (1.0%)	—

**Annex 15 Neonatal sepsis for the overall groups and according to the method of conception**

Complication	Twins				
	Total	Mode of conception			
		N=1311	SC N=825	MAR-total N=367	IVF N=174
Blood born sepsis	38 (2.9%)	19 (2.3%)	17 (4.6%)	6 (3.4%)	11 (6.2%)
Pneumonia	1 (0.1%)	1 (0.1%)	—	—	—
Meningitis	2 (0.2%)	1 (0.1%)	1 (0.3%)	—	1 (0.6%)
Triplets					
	N=184	N=30	N=143	N=101	N=26
Blood born sepsis	16 (8.7%)	3(10.0%)	12 (8.4%)	9 (8.9%)	3 (11.5%)
Pneumonia	1(0.5%)	—	1(0.7%)	1 (1.0%)	—
Meningitis	1(0.5%)	—	1 (0.7%)	1 (1.0%)	—
Urinary tract infection	1(0.5%)	1(3.1%)	—	—	—
Quadruplets					
	N=18	N=8	N=10	—	N=7
Blood born sepsis	3 (16.7%)	1 (12.5%)	2 (20.0%)	—	2 (28.6%)

**Annex 16 Neonatal hematologic disorders for the overall groups and according to the method of conception**

Complication	Twins					
	Total	Mode of conception				
	N= 1311	SC n=825	MAR-total N= 367	IVF N=174	IUI N=15	IOO N=178
Needed PRBCS	58 (4.4%)	26 (3.2%)	27 (7.4%)	11 (6.3%)	1 (6.7%)	15 (8.4%)
DIC	3 (0.2%)	2 (0.2%)	1 (0.3%)	—	—	1 (0.6%).
Anemia	2 (0.2%)	1 (0.1%)	1 (0.3%)	—	—	1 (0.6%).
Coagulopathy	1 (0.1%)	1 (0.1%)	—	—	—	—
Triplets						
	N=184	N=30	N=143	N=101	N=16	N=26
Needed PRBCs	52 (28.3%)	5 (16.7%)	42 (29.4%)	27 (26.7%)	7 (43.8%)	8 (30.8%)
DIC	2 (1.1%)	1 (3.3%)	1 (0.7%)	1 (1.0%)	—	—
Thrombocytopenia	1 (0.5%)	—	1 (0.7%)	—	—	1 (3.8%)
Quadruplets						
	N=18	N=8	N=10	N=3	—	N=7
Needed PRBCS	12 (66.7%)	8 (100.0%)	4 (40.0%).	—	—	4 (57.1%)

*Note.*

PRBCs: packed red blood cells; DIC: disseminated intravascular coagulation.

**Annex 17 Other neonatal complications for the overall groups and according to the method of conception**

Complications	Twins					
	Total N=1311	Mode of conception				
		SC N=825	MAR-total N=367	IVF N=174	IUI N=15	IOO N=178
Intestinal obstruction	1 (0.1%)	1 (0.1%)	—	—	—	—
Hydrops fetalis	3 (0.2%)	3 (0.4%)	—	—	—	—
Perinatal asphyxia	11 (0.8%)	5 (0.6%)	5 (1.4%)	2 (1.1%)	—	3 (1.7%)
Poor sucking	7 (0.5%)	5 (0.6%)	1 (0.3%)	—	—	1 (0.6%)
Vomiting	3 (0.2%)	2 (0.2%)	—	—	—	—
Anemia of prematurity	10 (0.8%)	5 (0.6%)	4 (1.1%)	2 (1.1%)	1 (6.7%)	1 (0.6%)
Renal failure	1 (0.1%)	1 (0.1%)	—	—	—	—
Apnea	18 (1.4%)	12 (1.5%)	6 (1.6%)	3 (1.7%)	2 (13.3%)	1 (0.6%)
Contact dermatitis	1 (0.1%)	1 (0.1%)	—	—	—	—
Gastro esophageal reflux	1 (0.1%)	1 (0.1%)	—	—	—	—
Dacryostitis	1 (0.1%)	1 (0.1%)	—	—	—	—
Shoulder dystocia	1 (0.1%)	1 (0.1%)	—	—	—	—
Thigh cellulitis	1 (0.1%)	—	1 (0.3%)	—	—	1 (0.6%)
Hand necrosis	1 (0.1%)	1 (0.1%)	—	—	—	—
Convulsion	6 (0.5%)	5 (0.6%)	1 (0.3%)	—	—	1 (0.6%)
Persistent vomiting	2 (0.2%)	—	2 (0.5%)	2 (1.1%)	—	—
Hypoxic ischemic encephalopathy	3 (0.2%)	1 (0.1%)	1 (0.3%)	—	—	1 (0.6%)
Foot necrosis	1 (0.1%)	1 (0.1%)	—	—	—	—
Dehydration	2 (0.2%)	2 (0.2%)	—	—	—	—
Erbs palsy	1 (0.1%)	—	1 (0.3%)	1 (0.6%)	—	—
Soft systolic murmur	1 (0.1%)	—	1 (0.3%)	—	—	1 (0.6%)
Hypoglycemia- infant of diabetic mother	1 (0.1%)	1 (0.1%)	—	—	—	—
Thrombosis in lower extremities	1 (0.1%)	1 (0.1%)	—	—	—	—
Brain edema	2 (0.2%)	1 (0.1%)	1 (0.3%)	1 (0.6%)	—	—
Subdural hygroma	1 (0.1%)	1 (0.1%)	—	—	—	—
<b>Triplets</b>						
	<b>N=184</b>	<b>N=30</b>	<b>N=143</b>	<b>N=101</b>	<b>N=16</b>	<b>N=26</b>
Perinata asphyxia	1 (0.5%)	1 (3.3%)	—	—	—	—
Anemia of prematurity	5 (2.7%)	—	3 (2.1%)	2 (2.0%)	—	1 (3.8%)
Apnea	3 (1.6%)	1 (3.3%)	2 (1.4%)	1 (1.0%)	1 (6.3%)	0 (0.0%)
Skull fracture	1 (0.4%)	1 (3.3%)	—	—	—	—
Dacryostitis	1 (0.4%)	—	1 (0.7%)	1 (1.0%)	—	—
Convulsion	1 (0.4%)	—	1 (0.7%)	1 (1.0%)	—	—
Bronchopulmonary dysplasia	1 (0.4%)	—	1 (0.7%)	1 (1.0%)	—	—
Aspiration pneumonia	1 (0.4%)	—	1 (0.7%)	1 (1.0%)	—	—
Brain edema	1 (0.4%)	1 (3.3%)	—	—	—	—
Subdural hygroma	2 (1.1%)	2 (6.7%)	—	—	—	—
<b>Quadruplets</b>						
	<b>N=18</b>	<b>N=8</b>	<b>N=10</b>	<b>N=3</b>	—	<b>N=7</b>
Anemia of prematurity	1 (5.6%)	—	1 (10.0%)	—	—	1 (14.3%)
Apnea	1 (5.6%)	1 (12.5%)	—	—	—	—

**Annex 18 Types of congenital abnormalities for the overall groups and according to the method of conception**

Abnormalities	Twins					
	Total N=1407	Mode of conception				
		SC N=894	MAR-total N=394	IVF N=194	IUI N=15	IOO N=185
Central nervous system	11 (0.8%)	7 (0.8%)	3 (0.8%)	1 (0.5%)	—	2 (1.1%)
Cardio-vascular	10 (0.7%)	6 (0.7%)	3 (0.8%)	2 (1.0%)	—	1 (0.5%)
Muscle skeletal	19 (1.4%)	12 (1.3%)	4 (1.0%)	2 (1.0%)	—	2 (1.1%)
Genitourinary	17 (1.2%)	9 (1.0%)	8 (2.0%)	4 (2.1%)	1 (6.7%)	3 (1.6%)
Cystic hygroma	1 (0.1%)	1 (0.1%)	—	—	—	—
Congenital hypothyroidism	1 (0.1%)	1 (0.1%)	—	—	—	—
Ichymosis	1 (0.1%)	—	1 (0.3%)	—	—	1 (0.5%)
Imperforated anus	1 (0.1%)	—	1 (0.3%)	—	—	1 (0.5%)
Others	12 (0.9%)	9 (1.0%)	3 (0.8%)	2 (1.0%)	—	1 (0.5%)
Triplets						
	N=200	N=32	N=155	N=108	N=17	N=30
Central nervous system	1 (0.5%)	—	1 (0.6%)	1 (0.9%)	—	—
Cardio-vascular	3 (1.5%)	2 (6.3%)	1 (0.6%)	1 (0.9%)	—	—
Muscle skeletal	2 (1.0%)	—	2 (1.3%)	2 (1.9%)	—	—
Genitourinary	3 (1.3%)	1 (3.1%)	2 (1.6%)	2 (1.9%)	—	—
Others	1(0.5%)	—	1 (0.6%)	—	1 (5.9%)	—
Quadruplets						
	N=23	N=8	N=15	N=4	—	N=11
Central nervous system	1 (4.3%)	—	1 (6.7%)	—	—	1 (9.1%)
Cardio vascular	2 (8.7%)	2 (25.0%)	—	—	—	—
Muscle skeletal	4 (17.4%)	—	4 (26.7%)	—	—	4 (36.4%)

**Annex 19 Types of congenital heart abnormalities for the overall groups and according to the method of conception**

Abnormalities	Twins					
	Total N=1407	Mode of conception				
		SC N=894	MAR-total N=349	IVF N=194	IUI N=15	IOO N=185
Congenital heart disease	2 (0.1%)	2 (0.2%)	—	—	—	—
Pulmonary stenosis	2 (0.1%)	—	2 (0.5%)	1(0.5%)	—	1(0.5%)
Ventricular hypertrophy	1 (0.1%)	—	1 (0.3%)	—	—	1(0.5%)
Small pulmonary valve	1 (0.1%)	—	1 (0.3%)	—	—	1(0.5%)
Pulmonary hypertension	2 (0.1%)	1(1.2%)	1 (0.3%)	—	—	1(0.5%)
Patent ductus arteriosus	2 (0.1%)	1(1.2%)	1 (0.3%)	1(0.5%)	—	—
Ventricular septal deviation	3 (0.2%)	1(0.1%)	2(0.5%)	2(1.0%)	—	—
Overriding aorta	1 (0.1%)	—	1(0.3%)	1(0.5%)	—	—
DTGA †	2 (0.1%)	—	1(0.3%)	1(0.5%)	—	—
Transposition of the great arteries	1 (0.1%)	1(0.1%)	—	—	—	—
Atrial septal defect	2 (0.2%)	2(0.2%)	—	—	—	—
Pulmonary atresia ‡	2 (0.2%)	1(0.1%)	—	—	—	—
Small morphologic LV §	1(0.1%)	—	—	—	—	—
<b>Triplets</b>						
	<b>N=200</b>	<b>N=32</b>	<b>N=155</b>	<b>N=108</b>	<b>N=17</b>	<b>N=30</b>
Ventricular septal deviation	2(1.0%)	1(3.1%)	1(0.6%)	1 (0.9%)	—	—
Tetralogy of fallot	1(0.5%)	—	1(0.6%)	1 (0.9%)	—	—
Pulmonary stenosis	1(0.5%)	—	1(0.6%)	1 (0.9%)	—	—
Proximal lap stenosis	1(0.5%)	1(3.1%)	—	—	—	—
<b>Quadruplets</b>						
	<b>N=23</b>	<b>N=8</b>	<b>N=15</b>	<b>N=4</b>	—	<b>N=11</b>
Ventricular septal deviation	1 (4.3%)	1 (12.5%)	—	—	—	—
Atrial septal defect	2 (8.7%)	2 (25.0%)	—	—	—	—

*Note.*

DTGA, D-transposition of the great arteries.

†missing data about mode of conception for one case.

‡ missing data about mode of conception for one case.

§missing data about mode of conception.

**Annex 20 Types of central nervous system abnormalities for the overall groups and according to the method of conception**

	<b>Twins</b>					
<b>Abnormalities</b>	<b>Total</b>	<b>Mode of conception</b>				
	<b>N=1407</b>	<b>SC N=894</b>	<b>MAR-total N=394</b>	<b>IVF N=194</b>	<b>IUI N=15</b>	<b>IOO N=185</b>
Hydrocephalus	3(0.2%)	2(0.2%)	1(0.3%)	1 (0.5%)	—	—
Micro cephalous	2(0.1%)	1(0.1%)	1(0.3%)	—	—	1 (0.5%)
Encephalocele	2 (0.1%)	2(0.2%)	—	—	—	—
Meningoencephalocel e	2(0.1%)	2(0.2%)	—	—	—	—
Anencephaly*	2(0.1%)	—	1(0.3%)	—	—	1 (0.5%)
<b>Triplets</b>						
	<b>N=200</b>	<b>N=32</b>	<b>N=155</b>	<b>N=108</b>	<b>N=17</b>	<b>N=30</b>
Hydrocephalus	1(0.5%)	—	1 (0.6%)	1 (0.9%)	—	—
<b>Quadruplets</b>						
	<b>N=23</b>	<b>N=8</b>	<b>N=15</b>	<b>N=4</b>	<b>—</b>	<b>N=11</b>
Hydrocephalus	1 (4.3%)	—	1 (6.7%)	—	—	1 (9.1%)

*Note.*

\* missing data about mode of conception for one case.

**Annex 21 Types of genitourinary abnormalities for the overall groups and according to the method of conception**

Abnormalities	Twins					
	Total N=1407	Mode of conception				
		SC N=894	MAR-total N=394	IVF N=194	IUI N=15	IOO N=185
Congenital nephrotic syndrome	1(0.1%)	1(0.1%)	—	—	—	—
Hydrocele	7(0.5%)	2 (0.2%)	5(1.3%)	4(2.1%)	1(6.7%)	0 (0.0%)
Undescended testicle	4(0.3%)	3(0.3%)	1(0.3%)	—	—	1 (0.5%)
Polycystic kidney	2(0.1%)	1(0.1%)	1(0.3%)	—	—	1 (0.5%)
Hypospadias	2(0.1%)	2(0.2%)	—	—	—	—
Small penis	2(0.1%)	1(0.1%)	1(0.3%)	—	—	1 (0.5%)
Triplets						
	N=200	N=32	N=155	N=108	N=17	N=30
Undescended testicle	1(5.0%)	—	1(0.6%)	1 (0.9%)	—	—
Hypospadias	1(5.0%)	1(33.3%)	—	—	—	—
Poly cystic kidney	1(5.0%)	—	1(0.6%)	1 (0.9%)	—	—
Ambiguous genitalia	1(5.0%)	—	1(0.6%)	1 (0.9%)	—	—
Sever chordate	1(5.0%)	—	1(0.6%)	1 (0.9%)	—	—

**Annex 22 Types of musculoskeletal abnormalities for the overall groups and according to the method of conception**

Abnormalities	Twins					
	Total	Mode of conception				
	N=1407	SC N=894	MAR-total N=394	IVF N=194	IUI N=15	IOO N=185
Inguinal hernia	1(0.1%)	1(0.1%)	—	—	—	—
Club foot	2(0.2%)	1(0.1%)	1(0.3%)	1 (0.5%)	—	—
Umbilical hernia	2 (0.1%)	1(0.1%)	1(0.3%)	—	—	1 (0.5%)
Developmental dysplasia of hip ¶	5 (0.4%)	3(0.3%)	1(0.3%)	1 (0.5%)	—	—
Micro jaw	1(0.1%)	1(0.1%)	—	—	—	—
Osteopetrosis	1(0.1%)	1(0.1%)	—	—	—	—
Syndactyly	2 (0.1%)	2(0.2%)	—	—	—	—
Hypochondro – plasia #	2(0.1%)	1(1.2%)	—	—	—	—
Polydactyl	1(0.1%)	—	1(0.3%)	—	—	1(0.5%)
Triangular face	1(0.1%)	1(0.1%)	—	—	—	—
Chest pecturs excavatum	1(0.1%)	1(0.1%)	—	—	—	—
Omphalocele §	1(0.1%)	—	—	—	—	—
Triplets						
	N=200	N=32	N=155	N=108	N=17	N=30
Inguinal hernia	—	—	—	—	—	—
Club foot	2(1.0%)	—	2(1.3%)	2 (1.9%)	—	—
Quadruplets						
	N=23	N=8	N=15	N=4	—	N=11
Developmental dysplasia of hip	2 (8.7%)	—	2 (13.3%)	—	—	2 (18.2%)
Club foot	2 (8.7%)	—	2 (13.3%)	—	—	2 (18.2%)

*Note.*

¶ missing data about mode of conception for one case.

# missing data about mode of conception for one case.

§missing data about mode of conception.

**Annex 23 Types of other abnormalities for the overall groups and according to the method of conception**

	<b>Twins</b>					
<b>Abnormalities</b>	<b>Total</b>	<b>Mode of conception</b>				
	<b>N=1407</b>	<b>SC N=894</b>	<b>MAR-total N=394</b>	<b>IVF N=194</b>	<b>IUI N=15</b>	<b>IOO N=185</b>
Syndromatic	2(0.1%)	2(0.2%)	—	—	—	—
Lower limb abnormality	2 (0.1%)	1(0.1%)	1(0.3%)	—	—	1 (0.5%)
Accessory nipples at areola	1(0.1%)	1(0.1%)	—	—	—	—
Mongolian spot	1(0.1%)	1(0.1%)	—	—	—	—
Low set ear	1(0.1%)	—	1(0.3%)	1 (0.5%)	—	—
Depressed nasal bridge	2 (0.1%)	1(0.1%)	1(0.3%)	1(0.5%)	—	—
Periauricular skin tag	1(0.8%)	1(0.1%)	—	—	—	—
Leg positional abnormality	1(0.1%)	1(0.1%)	—	—	—	—
Dysmorphic feature -very small eyes	1(0.1%)	—	1(0.3%)	1(0.5%)	—	—
Medial deviation in the big toe	1(0.1%)	1(0.1%)	—	—	—	—
<b>Triplets</b>						
	<b>N=200</b>	<b>N=32</b>	<b>N=155</b>	<b>N=108</b>	<b>N=17</b>	<b>N=30</b>
Hemangioma	1 (0.5%)	—	1 (0.6%)	—	1 (5.9%)	—

## انتشار تعدد المواليد في خمس مستشفيات مستهدفة في الضفة الغربية العواقب على صحة الأم والطفل

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### الملخص

هذه الرسالة تهدف إلى تحديد مدى انتشار ظاهرة تعدد المواليد، وطريقة الحمل سواء كانت تلقائية أو عن طريق استخدام التقنيات المساعدة على الإنجاب، وعواقبها على صحة الأم والمواليد الجدد، وذلك بين النساء الفلسطينيات في خمس مستشفيات مختارة في الضفة الغربية.

استهدفت هذه الدراسة الاسترجاعية خمس مستشفيات موزعة في جنوب ووسط وشمال الضفة الغربية. تضمنت هذه الدراسة بيانات جميع النساء اللواتي أنجبن مواليد توأم على قيد الحياة بعمر حمل أكثر أو يساوي 24 أسبوعاً وأطفالهن وذلك عن طريق مراجعة سجلاتهم الطبية خلال الفترة من يناير 2010م إلى ديسمبر 2011م. تمّ تسجيل ما مجموعه 912 ولادة توأم (820 ولادة توأم ثنائي و92 ولادة توأم ثلاثي ورباعي)، شملت الدراسة 896 حالة (808 منها توأم ثنائي و88 توأم ثلاثي ورباعي).

أُضح من هذه الدراسة أنّ 2.2% (41,244/912) من جميع الولادات كانت ولادات متعددة المواليد، من مجموع الولادات متعددة المواليد، 89.9% كانت ولادة توأم ثنائي و 10.1% كانت ولادة توأم ثلاثي ورباعي. أما بالنسبة لطريقة الحمل، 68.3% (700/478) من مجموع ولادات التوأم الثنائي كان نتيجة للحمل التلقائي، و 31.7% (700/222) كان نتيجة استخدام تقنيات المساعدة على الإنجاب. بينما 83.7% (80/67) من ولادات التوأم الثلاثي والرباعي كانت نتيجة استخدام تقنيات المساعدة على الإنجاب، و 16.3% (80/13) منهم كانت نتيجة الحمل التلقائي. تعدد المواليد الناتج عن الإخصاب في المختبر ((IVF) وتحفيز الإباضة باستخدام أدوية الخصوبة (IOO) من أكثر الطرق استخداماً، بينما كانت تقنية التلقيح داخل الرحم (IUI) أقل استخداماً.

نتيجة لمقارنة ولادات التوأم الثنائي الثلاثي من المجموعتين (الحمل التلقائي والحمل الناتج عن استخدام تقنيات المساعدة على الإنجاب) أضح أنّ النساء اللواتي أنجبن توأم ثنائي وثلاثي نتيجة

استخدام تقنيات المساعدة على الإنجاب كن الأصغر سناً، ولديهن عدد منخفض من محاولات الحمل الطبيعي بالنسبة لعدد المرات التي أنجبن فيها قبل حصول الحمل المتعدد، حيث أن لديهن تاريخ عقم، وكن الأكثر استخداماً للتطويق الوقائي للرحم. كما كشفت الدراسة أن النساء اللواتي أنجبن توأم ثنائي بعد استخدام تقنيات المساعدة على الإنجاب كن أكثر عرضة للولادة المبكرة (61.7% مقابل 51.5%) وكذلك كن أكثر عرضة للولادة القيصرية (78.3% مقابل 52.2%). وقد أظهرت الدراسة أن النساء اللواتي أنجبن توأم ثلاثي الناتج عن الحمل التلقائي كن أكثر عرضة للإصابة بمضاعفات فقر الدم (36.4% مقابل 19.6%) وارتفاع ضغط الدم (18.2% مقابل 5.2%). لم يتم تسجيل حالات وفاة في أي من المجموعات التي تم دراستها.

في المقابل، كان معدل عمر حمل التوأم الثنائي الناتج عن استخدام تقنيات المساعدة على الإنجاب أقل من التوأم الناتج عن الحمل التلقائي (35.4 أسبوعاً مقابل 36.1)، بالإضافة إلى انخفاض معدل الوزن عند هؤلاء الأطفال (2275.6 مقابل 2402.2 غم). في هذه المجموعة أيضاً كان هناك ارتفاع في نسبة الأطفال حديثي الولادة المولودين قبل الأوان أقل من (37 اسبوعاً) (61.7% مقابل 51.0%) وزيادة في عدد الأطفال المولودين بوزن أقل من (2500 غراماً) (62.4% مقابل 50.5%)، وكذلك تم إدخال المزيد من المواليد إلى وحدة العناية المركزة لحديثي الولادة (51.5% مقابل 39.6%)، كما أنهم احتاجوا إلى فترة استشفاء أطول في هذه المجموعة، بالإضافة إلى ارتفاع نسبة الأطفال الذين يعانون من اضطرابات الجهاز التنفسي (35.7% مقابل 26.4%)، وكانوا الأكثر احتياجاً للاستئواء (20.7% مقابل 11.0%). من بين مواليد التوأم الثلاثي، كان عمر الحمل (32.5 مقابل 32.3 أسبوعاً) ومعدل الوزن (1704.5 غم مقابل 1618.9 غم) متقارباً في المجموعتين. كانت نسبة الإصابة باضطرابات الجهاز التنفسي أعلى في مجموعة الحمل الناتج عن استخدام تقنيات المساعدة على الإنجاب (92.3% مقابل 83.3%)، وكذلك مضاعفات الدم (30.1% مقابل 16.7%)، والحاجة إلى العلاج بالاستئواء (60.1% مقابل 40.0%)، كما أنهم احتاجوا إلى فترة استشفاء أطول في هذه المجموعة. وقد أظهرت هذه الدراسة أن الآلية التي تمت فيها عملية الحمل لم تؤثر على معدل الوفيات بين مجموعتي التوأم الثنائي والثلاثي.

لقد أظهرت الدراسة أن العلاج باستخدام أدوية الخصوبة ترك تأثيراً سلبياً بشكل أقل على عمر الحمل، كما أنه ساهم في تقليل نسبة حدوث الولادة القيصرية مقارنة بالوسائل الأخرى في حالات الحمل

الثنائي ، في حين أنه يساهم في رفع معدل الوفيات في مجموعة التوأم الثلاثي. كان للعلاج عن طريق التلقيح داخل الرحم تأثيراً سلبياً على عمر الحمل ووزن المواليد ، كما أنه يساهم في ارتفاع مضاعفات ارتفاع ضغط الدم في حالات الحمل بتوأم ثنائي. كما أن العلاج باستخدام تقنية التلقيح داخل الرحم يساهم في ارتفاع نسبة حدوث تمزق في الغشاء الأمنيوتي (PPROM) قبل الأوان في حالات الحمل بتوأم ثلاثي.

من هنا، خُلصَتِ الدَّرَاسَةُ إلى أَنَّ ولادات التوأم الثنائي الناتج عن استخدام تقنيات المساعدة على الإنجاب أكثر عرضة لحدوث مضاعفات الولادة والمواليد كما أن لها نتائج عكسية على مواليد التوأم الثلاثي. والنتائج المتعلقة بنتائج الحمل والولادة والمواليد الجدد بعد استخدام وسيلة التلقيح داخل الرحم لا تسمح باستنتاج نهائي وتحتاج إلى مزيد من التأكيد: لذلك تُرْفَعُ توصيات لتبني سياسات تأخذ بعين الاعتبار تعدد المواليد في تقييم الإحصائيات الحيوية، وأن يتبنى اختصاصيو الإنجاب استراتيجيات تهدف إلى خفض معدلات تعدد المواليد الناتجة عن استخدام التقنيات المساعدة على الإنجاب. الكلمات المفتاحية: تعدد المواليد، معدل الانتشار، النتائج الصحية للأم، النتائج الصحية للمواليد.