

Perinatal Outcome Following Assisted Reproductive Technology Treatment at A Tertiary Fertility Center In Nepal.

Sanu Maiya Shrestha Pradhan, Renee Pradhan, Manisha Bajracharya, Anita Karki, Namuna Ghimire
Creators IVF Nepal, Satdobato, Lalitpur, Nepal

ISSN: 2976-1050 (Online)

ISSN : 2976-1042 (Print)

Received : 15 Jul, 2022

Accepted : 20 Aug, 2022

Funding Source : None

Conflict of Interest : None

Corresponding Author

Renee Pradhan
Creators IVF Nepal,
Satdobato, Lalitpur, Nepal.
Email: pradhanrenee@gmail.com

Copyright: The Author(s) 2022

This is an open access article under
the CC BY-NC License.



ABSTRACT

Introduction. Globally, an increasing number of babies have been born with the help of Assisted Reproductive Technology (ART) treatment. While most births after ART are uncomplicated, sometimes it is associated with adverse perinatal outcomes such as preterm birth, low birth weight and increased risk of congenital anomalies. Therefore, the objective of this study was to assess the perinatal outcomes in children born after assisted reproductive technologies at a tertiary fertility center in Nepal.

Methodology. This was a descriptive study which analyzed retrospective data collected from the medical record of a tertiary fertility center at Lalitpur, Nepal. Perinatal outcomes of total 201 births that resulted from various ART treatment that was conducted in the center from November 2015 till April 2021 have been included in this study. Univariate analysis was done in SPSS version 20.

Results. Altogether, there were 201 total births out of which 199 were live births and 2 were stillbirths. Among the live births around two-third (69.7%) were singleton deliveries and remaining one-third (30.4%) were multiple deliveries. More than 90% of study population had undergone Lower Segment Caesarean Section (LSCS). There were 263 live born babies resulting from 199 live births. More than half of the babies were born prematurely (50.19%). Low birth weight (LBW) and very low birth weight (VLBW) was seen among 36.50% and 7.22% babies respectively. Congenital abnormality was identified in 13 babies (4.94%) Four stillborn babies and eight neonatal deaths were reported. More adverse perinatal outcomes were seen among twins and triplets than singleton babies.

Conclusion. While most births were uncomplicated, certain extent of adverse perinatal outcomes among the ART conceived babies cannot be ignored. Vigilant monitoring of pregnancy conceived by ART treatment helps in improving the perinatal outcome.

Keywords: Assisted reproductive technology, Congenital anomalies, Low birth weight, Perinatal outcomes

INTRODUCTION

Around one in seven couples have difficulty conceiving and many of these couples may require Assisted Reproductive Technology (ART) treatments.¹ Advancements in the field of ART have helped realize the dreams of parenthood of many infertile couples. The first baby to be ever born by in-vitro fertilization (IVF) is Louise Brown born in 1978. Since then, approximately 6.5 million births have been achieved till 2012 worldwide through the use of ART services.²

Globally, infertility continues to be a persistent problem and the demand for ART services is ever growing.^{3,4} It presents significant public health challenges due to the substantial risk for multiple birth delivery and preterm birth, which are associated with poor maternal and fetal health outcomes. For this reason, it is important to monitor the development and effectiveness of ART services in Thailand. Objective To analyze the trends of ART services in

Citation

Shrestha Pradhan SM, Pradhan R, Bajracharya M, Karki A, Ghimire N. Perinatal Outcome Following Assisted Reproductive Technology Treatment at A Tertiary Fertility Center In Nepal. 2022;01(01):30-36.

Thailand between 2008 and 2014. **Methods** ART clinics in Thailand are required to submit data to the Royal Thai College of Obstetricians and Gynecologists via the National Reporting System. The data from 2008 to 2014 were collected and analyzed. **Results** The number of ART centers was increased from 35 to 47. The total fresh ART cycles were also increased from 3,723 to 6,516. The percentage values of intracytoplasmic sperm injection (ICSI) In context of Nepal, IVF services was started in 2004.⁵

While ART has helped minimize the burden of infertility faced by many, it is sometimes associated with risks such as multiple births, preterm birth, low birth weight which are related to adverse maternal and fetal health outcomes (3) it presents significant public health challenges due to the substantial risk for multiple birth delivery and preterm birth, which are associated with poor maternal and fetal health outcomes. For this reason, it is important to monitor the development and effectiveness of ART services in Thailand. **Objective** To analyze the trends of ART services in Thailand between 2008 and 2014. **Methods** ART clinics in Thailand are required to submit data to the Royal Thai College of Obstetricians and Gynecologists via the National Reporting System. The data from 2008 to 2014 were collected and analyzed. **Results** The number of ART centers was increased from 35 to 47. The total fresh ART cycles were also increased from 3,723 to 6,516. The percentage values of intracytoplasmic sperm injection (ICSI). Studies have been reported from various parts of the world that analyzed the perinatal outcome of ART treatment. However, there is a lack of sufficient knowledge on perinatal outcome in ART treatment in Nepal. Therefore, this study was undertaken with an aim to assess the perinatal outcomes after assisted reproductive technology treatment at a tertiary fertility center in Nepal.

METHODOLOGY

This is a descriptive retrospective study that was carried out at Creator's IVF Nepal Pvt. Ltd. (CIVF), a fertility center at Lalitpur, Nepal. The Embryo Transfer (ET) cycles that resulted in live birth or stillbirth from November 2015 to April 2020 were included in the study.

Information related to demographic and clinical characteristics of patients and the respective perinatal outcomes were collected from the medical record section. Information on the perinatal outcomes were collected by the clinical nurses of CIVF by following up the patients through telephone-based interviews as a part of ongoing medical record activity.

According to The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary

on ART Terminology, 2009, live birth has been defined as the complete expulsion or extraction of a product of fertilization from the mother, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life such as heart beat, umbilical cord pulsation, definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached (6).

Perinatal outcomes included the variables like period of gestation at delivery, birth weight of baby, presence of any congenital anomaly in the baby, still birth and neonatal death. Birth was categorized as preterm birth and full-term birth. In this study, pre-term birth was defined as any live birth or still birth where delivery occurred after 28 weeks of gestation but before 37 completed weeks of gestation. Full-term birth was defined as a live birth or stillbirth that occurred between 37 and 42 completed weeks of gestation.

Birth weight of live born babies was categorized into very low birth weight (VLBW), low birth weight (LBW) and normal birth weight. Birth weight less than 1500 grams was referred as very low birth weight (VLBW). Low birth weight was defined having birthweight less than 2500 grams. Normal birthweight was defined as birthweight having 2500 grams or more.⁶

Neonatal death (NND) was defined as death among livebirths within the first 28 days of life. It was subdivided into early neonatal death and late neonatal death. Death occurring between 0 and 7 completed days of life was referred as early neonatal death whereas death after 7 days and before 28 completed days of life were considered as late neonatal death.⁷

Stillbirth was defined as the death of a fetus prior to the complete expulsion or extraction from the mother after 28 completed weeks of gestational age. The death is determined by the fact that, after such separation, the fetus does not breathe or show any other evidence of life, such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles.⁸

Perinatal death was defined as a stillbirth or neonatal death of at least 20 weeks' gestation or at least 400 grams' birthweight.⁹

Congenital anomaly was defined as structural or functional anomaly that can be identified during general prenatal checkup, at birth, or sometimes may only be detected later in infancy.¹⁰

Data entry was done in MS-Excel, which was then exported to IBM SPSS (Statistical Package for the Social Sciences) version 20 for further data management and analysis. Descriptive analysis was computed. Univariate analysis

was done in which continuous variables were presented as mean and standard deviation whereas categorical variables were represented in frequency and percentages.

RESULTS

Altogether, 256 total births resulted from ART (IVF/ICSI) treatments were recorded over the study period. Among the total 256 births, information about perinatal outcome of 55 births were incomplete. Hence were excluded. Therefore, this study presents perinatal outcome of 201 total births. Out of 201 total deliveries, 199 were live births resulting in 263 live born babies (139 singletons, 109 twins and 15 triplets). Additionally, there were two stillbirths which resulted in four stillborn babies.

Demographic and clinical characteristics

Overall, 201 embryo transfer (ET) cycles that resulted in either live birth or still birth were analyzed. The average age of women was 32.96 years. The age of women ranged from 20 to 47 years. The proportion of primary infertility was more than secondary infertility. The mean duration of infertility in the study population was 5.13 years. Female factor and unexplained infertility were major indication for ART treatment. Majority of women (70.6%) had undergone autologous cycles. About 21.4% women underwent oocyte recipient cycles and followed by embryo recipient cycles (i.e., 8.0%) respectively. Conventional IVF was mostly used technique of fertilization (71.01%). More fresh embryo transfers (i.e., 88.6%) were performed than frozen ET (i.e., 11.4%). The mean number of embryos transferred was 3.34. (Table 1)

Table 1. Demographic and clinical characteristics (n=201)

| Characteristics | Frequency | Percentage (%) |
|---|-------------------------|----------------|
| Age of wife (Mean \pm SD) | 32.96 \pm 4.83 years | |
| Type of infertility | | |
| • Primary | 122 | 60.7% |
| • Secondary | 79 | 39.3% |
| Duration of infertility (Mean \pm SD) | (5.13 \pm 3.89) years | |
| Cause of infertility | | |
| • Female factor | 88 | 43.8% |
| • Unexplained | 80 | 39.8% |
| • Male factor | 31 | 15.4% |
| • Combined male-female factor | 2 | 1.0% |
| Type of ART treatment | | |
| • Autologous Cycle | 142 | 70.6% |
| • Oocyte recipient cycle | 43 | 21.4% |
| • Embryo recipient cycle | 16 | 8.0% |

| Type of fertilization *(n=169) | | |
|--------------------------------|------------------|-------|
| • IVF | 120 | 71.0% |
| • ICSI | 49 | 29.0% |
| Type of embryo transfer | | |
| • Fresh | 178 | 88.6% |
| • Frozen | 23 | 11.4% |
| Number of embryos transferred | 3.34 \pm 0.915 | |

* includes fresh autologous and fresh oocyte recipient cycles only

Birth plurality and mode of delivery of the 201 deliveries, around two-third were singleton deliveries and the remaining one third were multiple births (twin delivery 27.9% and triplet delivery 2.5%). Majority of study population (93%) underwent Lower Segment Cesarean Section (LSCS) and the rest of 6.5% women had vaginal delivery.

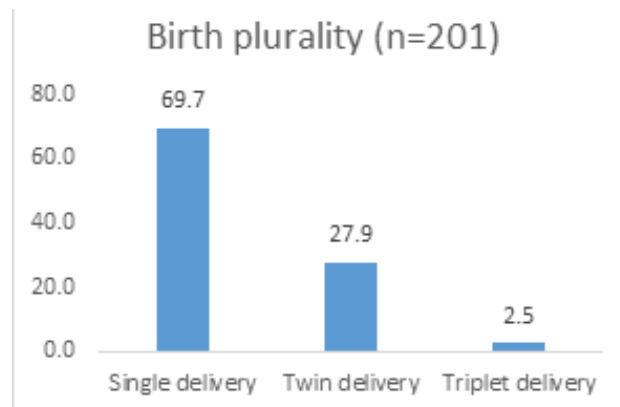


Figure 1: Birth plurality

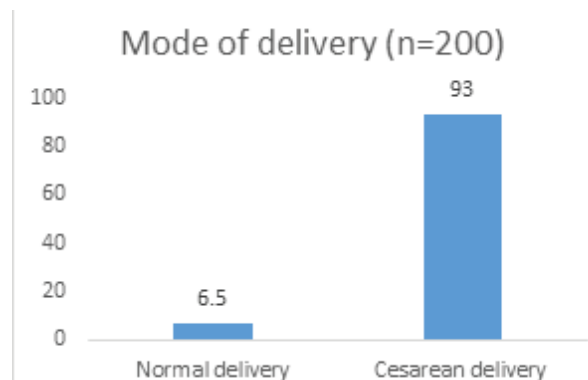


Figure 2: Mode of delivery

Perinatal outcomes of live born babies (n=263)

Table 2 shows information on the perinatal outcomes of 263 live born babies. More than half i.e., 50.19% babies were born prematurely and the rest of 49.80% babies had term delivery. Most of the babies were male babies (55.89) and remaining (44.10%) percent were female babies.

Majority of deliveries were singleton (69.7%) followed by twins (27.9%) and the rest of few were triplets (2.5%) respectively. The average birth weight of the babies was 2500 grams (SD=700). Majority of the babies (56.27%) had normal birth weight whereas 36.50% babies had low birth weight and 7.22% had very low birth weight. Congenital abnormality was identified in only 13 babies.

| Characteristics | Frequency(n) | Percentage (%) |
|---|--------------|----------------|
| Period of gestation at the time of delivery | | |
| Pre-term | 132 | 50.19% |
| Term | 131 | 49.80% |
| Sex of baby | | |
| Male | 147 | 55.89% |
| Female | 116 | 44.10% |
| Birthweight | | |
| Very low (VLBW) | 19 | 7.22% |
| Low (LBW) | 96 | 36.50% |
| Normal | 148 | 56.27% |
| Congenital abnormality | | |
| Yes | 13 | 4.94% |
| No | 250 | 95.05% |

Comparison of perinatal outcomes by birth plurality

Table 3 provides information on comparison of perinatal outcomes by plurality. Out of 139 singletons deliveries, male babies were more than female babies (56.1% vs 43.9%). In case of twins, there were more males (56.9%) than females (43.1%). In triplets, females were more than males i.e., 56.3% v/s 46.7%. In singleton pregnancies, more than two-third had term delivery i.e., 71.22% whereas in one third there was premature delivery. In case of twin's pregnancy, less than one-third (29.35%) women delivered after 37 completed weeks. All the triplets were born prematurely.

Regarding birthweight, majority singletons (84.9%) had normal birth weight followed by low birth weight and very low birth weight i.e., 13.7% and 1.4% respectively. Most of the twins (i.e., 62.4%) had low birth weight whereas in remaining twins (i.e., 27.5%) were born with normal birth weight. Low birth weight was reported in 60% triplets whereas very low birth weight accounted for 40% of triplets.

More congenital anomalies like cardiac abnormality, cleft palate, hydrocephalous was seen among singletons than twins and triplets (13.3%, 5.5%, and 3.6%) respectively.

| Characteristics | Singletons | | Twins | | Triplets | |
|---|------------|-------|---------|-------|----------|-------|
| | (n=139) | % | (n=109) | % | (n=15) | % |
| Sex of baby | | | | | | |
| • Male | 78 | 56.1% | 62 | 56.9% | 7 | 46.7% |
| • Female | 61 | 43.9% | 47 | 43.1% | 8 | 53.3% |
| Period of gestation at the time of delivery | | | | | | |
| • Premature | 40 | 28.8% | 77 | 70.6% | 15 | 100% |
| • Term | 99 | 71.2% | 32 | 29.4% | 0 | 0% |
| Birthweight | | | | | | |
| • Very low birthweight | 2 | 1.4% | 11 | 10.1% | 6 | 40% |
| • Low birth weight | 19 | 13.7% | 68 | 62.4% | 9 | 60% |
| • Normal birth weight | 118 | 84.9% | 30 | 27.5% | 0 | 0% |
| Congenital abnormality | | | | | | |
| • Yes | 5 | 3.6% | 6 | 5.5% | 2 | 13.3% |
| • No | 134 | 96.4% | 103 | 94.5% | 13 | 86.7% |

Perinatal deaths

Altogether, 201 total births took place out of which 199 were live births. There were 4 stillborn babies and 8 neonatal deaths. Out of 8 neonatal deaths, 3 were early (37.5%) and 5 were late neonatal deaths (62.5%).

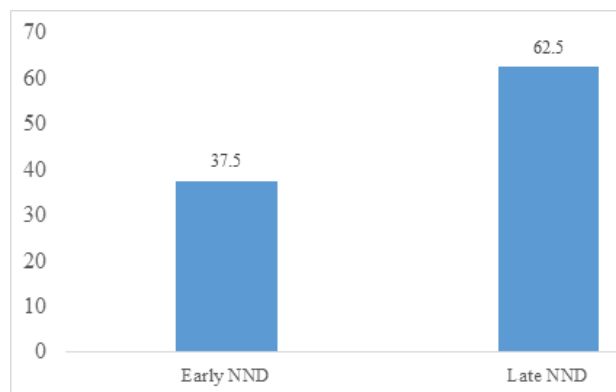


Figure 3: Type of neonatal deaths

DISCUSSION

The use of Assisted Reproductive Technology (ART) treatment has significantly increased over the past few decades. ART has enabled many infertile couples to become pregnant. Although most births after ART are uncomplicated, it has been linked with adverse perinatal outcomes among babies born by the treatment. In context of Nepal, in recent times ART treatment is emerging. But there is no adequate research in the field of ART treatment. Prior to this study, the perinatal outcome of children born as a result of assisted reproductive technology treatment has not been investigated. This study presents the perinatal outcomes of babies born by different types of ART treatment which used woman's own oocytes, donated oocytes and donated embryos. The study was conducted in a tertiary fertility centre in Nepal over a period of four and half years.

In our study, around two-third were singleton births and remaining one-third were multiple births. Similar proportions were reported in a study by Valvi et. al. where 63.3 % women had singleton pregnancy and 36.67% had twin pregnancy.¹¹ In another study by Narayan et. al among 504 live born infants, almost half were twins i.e. 48.8% as compared to singletons i.e. 51.2%. The prevalence of multiple births was higher than reported in our study.¹²

In our study, 90% women underwent cesarean section. A study by Morales et. al also reported similar findings in which Caesarean section accounted for 90% as mode of delivery.¹³ It is important to note that in our study, most

women had undergone elective CS in the view of IVF treatment, and the relevant obstetric complications which were due to underlying conditions of the patients.

Previous studies have reported the proportion of neonates born with low birth weight has been reported as 48.1%, 36.5%, 36.7% which is comparable to our study i.e. 43.72%.^{12,14,15} 190 (37.7%). The average birthweight of neonates reported in our study was 2500 ± 700 grams. In a study by Godoy Morales, which reported perinatal complications in children born after assisted reproduction treatments reported average birthweight of 2592.7 grams in 124 neonates comparative, retrospective and cross-sectional study of patients from 2008 to 2018 at the Hospital Angeles, Mexico City (cases).¹³ Both our study and Morales involved patients treated with ART, either by own embryos, donated embryos or by oocyte donation which could explain the similarity in the findings. Likewise, Silva et. al reported neonates born after ART techniques had lower birth weight of 2832±gms.¹⁶ These findings are similar to the finding of our study. In a study by Lei et. al, 22% singleton had low birth weight compared to 49.9% twins.¹⁵ Likewise, in 2019 Australia and New Zealand reported that approximately one in ten (10.6%) of the 16,704 live born babies were of low birthweight compared to 65.9% twins (9). Our study reported similar findings with 15.09% singletons born weighing less than 2500 grams and nearly three- fourths i.e., 72.47% twins having low birth weight.

Our study reported the prevalence of pre-term birth to be 50.19% which is slightly higher than the prevalences reported by Zhu et. al (38.8%), Sivia et. al (34.8%), Narayan (47.7%), Valvi et. al (43.3%) Lei et. al (38.7%).^{11,12,14-16} a major tertiary care hospital after approval of the institutional ethics committee. A retrospective analysis of maternal and perinatal outcome of 30 cases of ART conception from the year 2014 to 2018 was done. Results: The mean age of women enrolled into present study was 37.6 years and most common age group was 30-50 years. The main cause of infertility was unexplained (40%. In our study, more than two third twins i.e., 70.64% were born prematurely. A study by Baxi et. al. which analyzed spontaneous conceived and assisted multifetal pregnancies reported premature birth among 88.9% twin pregnancies.¹⁷ Moreover, all the triplets were born prematurely. The national report on Assisted reproductive technology in Australia and New Zealand 2019 also reported premature delivery among all higher order multiple births.⁹

In our study, the prevalence of congenital abnormality was 3.80%. Congenital abnormalities were detected in 20 of the cohort i.e., 3.9% as per the findings of Narayan et. al among 504 consecutive live born infants over a two-year period (12) 190 (37.7%). Highest proportion of congenital

abnormality was seen among triplets followed by twins than singletons (13.3%, 5.50% and 3.6%) respectively. Zhang et. al reported prevalence of any birth defect in ART offspring to be 5.5%.¹⁸

Likewise, a population-based cohort study linking ART cycles reported to the Society for Assisted Reproductive Clinic Outcome Reporting System (SART) by Luke et. al established the prevalence of birth defects to be 1.9% among singletons, and 3.3% among twins (19) whereas the prevalence of congenital malformation was 3.4% among singletons and 5.3% among twins in another study by Henningsen et. al.²⁰

Our study reported 2 stillbirths among 201 total births i.e., 1.99% and 8 neonatal deaths among 199 total live birth i.e., 4.02% and 12 perinatal deaths among 201 total births i.e., 5.9%. In a retrospective study by Valvi et. al, there were 4 stillbirths accounting 9.76%, 12.2% neonatal death rate and 21.95% perinatal death rate, which is higher than our study population. However, the study by Valvi et. al only included 30 cases (11) a major tertiary care hospital after approval of the institutional ethics committee. A retrospective analysis of maternal and perinatal outcome of 30 cases of ART conception from the year 2014 to 2018 was done. Results: The mean age of women enrolled into present study was 37.6 years and most common age group was 30-50 years. The main cause of infertility was unexplained (40%). Likewise, a total of 30 (5.9%) out of 504 reported neonates suffered mortality in a study by Narayan et. al 190 (37.7%).¹²

Our study had certain limitations. Perinatal outcomes could not be reported from patients who could not be contacted and were lost to follow up. Further, the perinatal outcomes were self-reported by women themselves and information were not collected from official records from the hospitals where babies were delivered, which could lead to underreporting or over reporting of adverse perinatal outcomes. Certain extent of recall bias may exist even though the patients were contacted for delivery outcomes around their anticipated delivery date.

CONCLUSION

While most births were safe and without major complications, certain extent of adverse perinatal outcomes among the ART conceived babies cannot be ignored. As expected, twins and triplet neonates were more likely than singletons to experience adverse perinatal outcomes than singleton baby. In order to lessen the perinatal complications associated with ART, elective single embryo transfer may be considered whenever possible to avoid multifetal gestation. Close monitoring of ART pregnancy should be done to minimize the risks of adverse perinatal outcomes.

REFERENCES

1. Infertility - NHS [Internet]. [cited 2022 Jul 27]. Available from: <https://www.nhs.uk/conditions/infertility/>
2. Almaslami F, Aljunid SM, Ghailan K. Demographic determinants and outcome of in vitro fertilization (IVF) services in Saudi Arabia. *J Int Med Res.* 2018 Apr;46(4):1537–44. PMID: 29350090 PMCID: [PMC6091848](#). DOI: [10.1177/0300060517749329](#)
3. Chiamchanya C, Pruksananonda K. Development of assisted reproductive technology services in Thailand between 2008 and 2014 before the new law: Results generated from the National ART Registry, Royal Thai College of Obstetricians and Gynecologists. *Asian Biomedicine.* 2020 Jun 4;13:189–96.
4. Progress in Reproductive Health Research. Available from: <https://www.who.int/reproductivehealth/publications/infertility/progress63.pdf>
5. Calls to make In Vitro Fertilisation affordable [Internet]. [cited 2020 Aug 25]. Available from: <https://kathmandupost.com/national/2018/06/03/calls-to-make-in-vitro-fertilisation-affordable>
6. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Human Reproduction.* 2009 Nov 1;24(11):2683–7. PMID: 19801627. DOI: [10.1093/humrep/dep343](#)
7. Pathirana J, Muñoz FM, Abbing-Karahagopian V, Bhat N, Harris T, Kapoor A, et al. Neonatal death: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine.* 2016 Dec;34(49):6027–37. PMID: 27449077. PMCID: PMC5139812. DOI: [10.1016/j.vaccine.2016.03.040](#)
8. Adhikari R, Rishal P, Gupta R. Infertility, childlessness, and healthcare seeking in resource-poor settings in Nepal. 67.
9. Newman JE, Paul RC, Chambers GM. Assisted reproductive technology in Australia and New Zealand 2019 :93.
10. CDC. 1.4 Congenital Anomalies - Definitions [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2022 Jul 26]. Available from: <https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-1/chapter1-4.html>
11. Valvi D, Swaminathan G. Maternal and perinatal outcome following assisted reproductive technology in a tertiary care centre: a retrospective study. *Int J Reprod Contracept Obstet Gynecol.* 2019 Apr 29;8(5):1745.
12. Narayan S, Rana K, Sharma M, Sharma R, Talwar P, Kapur K, et al. Profile of Live-born Infants of In-vitro Fertilisation. *Med J Armed Forces India.* 2010 Jan;66(1):18–21. PMID: 27365697 PMCID: [PMC4920915](#). DOI: [10.1016/S0377-1237\(10\)80085-1](#)
13. Morales G. Perinatal complications of children born after assisted reproduction treatments, is there a difference with those born by spontaneous pregnancy? results in 2 centers. *International Journal of Pregnancy & Child Birth.* 2019;5(5).
14. Zhu L, Zhang Y, Liu Y, Zhang R, Wu Y, Huang Y, et al. Maternal and Live-birth Outcomes of Pregnancies following Assisted

- Reproductive Technology: A Retrospective Cohort Study. *Sci Rep*. 2016 Dec;6(1):35141. PMID: 27762324. PMCID: [PMC5071829](#). DOI: [10.1038/srep35141](#)
15. Lei LL, Lan YL, Wang SY, Feng W, Zhai ZJ. Perinatal complications and live-birth outcomes following assisted reproductive technology: a retrospective cohort study. *Chin Med J (Engl)*. 2019 Oct 20;132(20):2408–16. PMID: 31634242. PMCID: [PMC6831076](#). DOI: [10.1097/CM9.0000000000000484](#)
16. Silva S, Machado H. Heterosexual couples' uses and meanings of ovarian stimulation: Relatedness, embodiment and emotions. *Health (London)*. 2011 Nov;15(6):620–32. PMID: 21177709DOI : [10.1177/1363459310364161](#)
17. Baxi A, Kaushal M. Outcome of twin pregnancies conceived after assisted reproductive techniques. *J Hum Reprod Sci*. 2008;1(1):25. PMID: 19562060.PMCID: [PMC2700680](#). DOI: [10.4103/0974-1208.39593](#)
18. Zhang L, Zhang W, Xu H, Liu K. Birth defects surveillance after assisted reproductive technology in Beijing: a whole of population-based cohort study. *BMJ Open*. 2021 Jun 1;11(6):e044385. PMID: 34162637. PMCID: [PMC8231031](#). DOI: [10.1136/bmjopen-2020-044385](#)
19. Luke B, Brown MB, Wantman E, Forestieri NE, Browne ML, Fisher SC, et al. The risk of birth defects with conception by ART. *Human Reproduction*. 2021 Jan 1;36(1):116–29. PMID: 33251542. PMCID: [PMC8679367](#). DOI: [10.1093/humrep/deaa272](#)
20. Henningsen AKA, Bergh C, Skjaerven R, Tiitinen A, Wennerholm UB, Romundstad LB, et al. Trends over time in congenital malformations in live-born children conceived after assisted reproductive technology. *Acta Obstetrica et Gynecologica Scandinavica*. 2018;97(7):816–23. PMID: 29572867DOI: [10.1111/aogs.13347](#)